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An fMRI-study on single-sided deafness: Spectral-temporal properties and side of stimulation modulates hemispheric dominance

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ABSTRACT

Objective: Our main aim was to investigate the blood oxygenation level dependent (BOLD) response to monaural and binaural speech- and non-speech stimuli as measured with fMRI in subjects with single-sided deafness and in normal hearing controls. We hypothesised that the response to monaural stimulation in both normal hearing subjects and persons with single-sided deafness would vary with the complexity and nature of the stimuli and the side of stimulation.

Design: Patients with left- and right single-sided deafness and controls with normal hearing receiving either binaural or monaural stimuli were tested using speech and non-speech auditory stimuli in an event-related fMRI experiment.

Study sample: Twenty-two patients with single-sided deafness after treatment for vestibular schwannoma and 50 normal hearing controls.

Results: Normal hearing persons receiving right side monaural stimuli activate bilateral temporal regions. Activation following left side monaural stimulation is more right lateralized. Persons with single-sided deafness respond similarly to controls to monaural stimulation. Persons with right side single-sided deafness show activation of frontal cortical regions not seen in persons with left side single-sided deafness following speech stimuli. This is possibly related to increased effort and more frequently reported problems with communication. Right side single-sided deafness is related to increased activation of areas usually related to processing of degraded input, including the thalamus.

Conclusion: Hemispheric dominance following monaural auditory stimulation is modulated by the spectral-temporal properties of the stimuli and by which ear is stimulated. Differences between patients with right- and left side deafness suggests that right side deafness is related to increased activation of areas involved in processing of degraded input.

1. Introduction

Historically, the consequences of monaural auditory deprivation have not been given much attention, as they were believed to be minimal. However, more recent studies have revealed that the effect of unilateral hearing loss (UHL) and single-sided deafness (SSD)on processing of auditory stimuli may have far reaching consequences affecting quality of life (QoL) (Harkonen et al., 2017) as well as educational outcomes and listening effort (Lewis et al., 2016). It may also affect language development in children (Anne et al., 2017). UHL/SSD is quite common in new-borns (0.5/1000 births) (Zhang et al., 2018), and schoolchildren (3–5%) (Vila and Lieu, 2015). These conditions may also be caused by trauma, otological diseases, degeneration and retro-cochlear pathologies such as vestibular schwannoma (VS) (Pross et al., 2015). Thus, the incidence increases with age (Vila and Lieu, 2015; Tharpe and Sladen, 2008). Recent studies also suggest that

Abbreviations: UHL, Unilateral hearing loss; SSD, Single sided deafness; fMRI, functional magnetic resonance imaging; BOLD, blood oxygenation level dependent

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the prevalence of UHL is on the rise (Shargorodsky et al., 2010) (Vila and Lieu, 2015).

In normal hearing, information projects ipsilaterally and contralaterally through the ascending auditory pathway, providing binaural inputs to both auditory cortices (Chang et al., 2016). Disrupted function in one ear leads to asymmetric input from the peripheral auditory system to the brainstem and central auditory pathways. This causes deficits in hearing functions that rely on binaural input and performance, leading to higher-order central dysfunction in psychoacoustic abilities (Pross et al., 2015). Thus, persons with UHL typically report problems with sound source localization, speech perception in noise as well as an increase in listening effort (Gatehouse and Speech, 2004) (Pross et al., 2015).

Reorganization following UHL/SSD has been found in several studies using different techniques, close to hearing loss (HL) onset and several years later (Hanss et al., 2009) in developing and mature auditory systems (Khosla et al., 2003). In electrophysiological studies, late latency auditory evoked potentials (AEPs) revealed neurophysiological changes in both amplitude and time course of the activation pattern to non-speech sound in those with left side HL but not in those with right side HL (Hanss et al., 2009). Hence, it seems the side of the HL influence the central auditory plasticity.

In addition to reports of bilateral cortical activity similar to that following binaural stimulation of normal hearing controls, the main finding from a recent review was that UHL/SSD not only affects regions of the brain known to be involved in auditory processing, but even non-auditory regions and structures (Heggdal et al., 2016). However, previous studies were carried out in cohorts with less than optimal control for etiology, hearing loss (HL) configuration and duration of HL (Heggdal et al., 2016) (Pross et al., 2015) (Eggermont, 2017). A few issues to be considered were uncovered when reviewing the literature. Regarding degree of HL, some studies, such as Burton et al. (Burton et al., 2013) included subjects with hearing as good as 40 dB HL in the affected ear, while others, such as Scheffler et al., (1998) reported a "total loss" of hearing in the affected ear. We suggest that degree of HL and duration with HL is a key point when considering reorganization of the auditory pathways (Pross et al., 2015). Even in subjects with HL far less than profound, Burton et al., (2013) found signs of cortical reorganization. Therefore, we must take into consideration that a plastic process could start long before the ear is defined as deaf or with profound HL.

Previous studies have suggested that bilateral cortical activity following auditory stimulation of the unaffected ear in subjects with UHL/SSD are signs of cortical reorganization (Scheffler et al., 1998) (Chang et al., 2016). This is based upon the assumption that the normal cortical response to monaural stimulation in bilateral normal hearing is asymmetric, due to a mainly contralateral routing of signals from the peripheral auditory system. This would suggest that while the dichotic nature of real world listening environments drive both hemispheres to alternate or concomitantly dominance in normal hearing subjects, SSD could force a permanent hemispheric dominance (Pross et al., 2015; Kaneko et al., 2003).

Previous studies on patients with SSD have mainly utilized non-complex stimuli such as pure tones (Scheffler et al., 1998; Schmithorst et al., 2005; Bilecen et al., 2000), and noise-like sound bursts (Burton et al., 2013; Burton et al., 2012; Firszt et al., 2013; Propst et al., 2010). We suggest using monaural stimulation that challenges the brains differential processing of speech versus non-speech stimuli in normal hearing subjects. Thus, we hypothesize that lateralization is modulated by the nature of the stimuli and by which ear is stimulated (Sequeira Sdos et al., 2008; Specht and Reul, 2003) (Zatorre and Belin, 2001).

The present study applies a "sound morphing" fMRI-paradigm developed by Specht et al. (Specht et al., 2009; Specht et al., 2005). This paradigm uses white noise that is gradually changed, in seven steps, to either a consonant-vowel speech sound or a guitar or piano sound and allows for separating speech sensitive areas from areas generally responding to auditory signals. This paradigm has identified an area of the left superior temporal sulcus (STS) that demonstrates an increase in leftward lateralization as a sound change into a speech sound not seen for other auditory stimuli (Specht et al., 2009). A supporting role of the left premotor cortex in the perception of distorted and degraded speech signals has also been seen (Osnes et al., 2011) (Zhang et al., 2018). With the findings of recent literature reviews (Heggdal et al., 2016; Eggermont, 2017) in mind, the present study includes patients with complete SSD caused by vestibular schwannoma (VS). Considering previous reports on the time course of reorganization in UHL/SSD (Chang et al., 2016; Bilecen et al., 2000; Burton et al., 2012), suggesting that the plastic process is ongoing for at least a year following hearing loss onset, all patients had been deaf in one ear for at least two years.

Our main aim was to investigate the response to monaural versus binaural stimuli of various temporal-spectral complexities, and how these processes are affected by SSD. We hypothesize that the BOLD-response to monaural stimulation in both normal hearing subjects and persons with SSD depends on the complexity and nature of the stimuli used, and the side of stimulation.

2. Design and study sample

2.1. Subjects

Patients with SSD following treatment of VS were recruited and tested while in the clinic for ordinary follow-up appointments. Inclusion criteria were complete deafness (pure tone thresholds 0.25–8 kHz > 120 dB HL) in one ear following treatment of VS, and normal hearing (pure tone average for frequencies 0.5, 1, 2 & 4 kHz [PTA] ≤ 25 dB HL) in the contralateral ear. Exclusion criteria were metal or ferromagnetic implants or braces, other known serious neurological or psychiatric illnesses or pregnancy. Twenty-two patients (9 males) were included, aged 25–62 years (M = 48, SD = 10.7). Twelve patients had right side HL. HL duration ranged from two to 16 years (M = 6, SD = 4.3) and was defined as years with complete loss of hearing in one ear, as confirmed by pure tone audiometry in patient records. Twelve patients had received microsurgical treatment of the tumour. Four patients had been treated with gamma knife therapy. The remaining six patients had received both treatments sequentially. A group of normal hearing persons were recruited to a control group. Inclusion criteria were normal hearing in both ears (≤ 25 dB HL at frequencies 0.25–8 kHz). Exclusion criteria were metal of ferromagnetic implants or braces, known neurological or psychiatric illness or pregnancy. Fifty persons (25 males) were included in the control group, aged 23–58 years (M = 36, SD = 10).

All subjects were right handed. Handedness was determined according to the Edinburgh Inventory using an exclusion criterion set to 13 of 15 possible points (Annett, 1970). All subjects signed a letter of consent prior to testing. The Norwegian Regional Committees for Medical and Health Research Ethics provided advance approval for the project (Project reference: 2013/1282-3).

2.2. Groups formed by subjects

Patients formed two groups based on right- or left side SSD. Three groups of normal hearing controls were formed. These were those that received binaural (n = 21), left-side (n = 14) or right side (n = 15) stimulation. Each subject only performed the fMRI-experiment once.

2.3. Self-assessment of communication (SAC)

Patients and controls completed a questionnaire measuring their self-assessed ability to communicate verbally in quiet and adverse listening conditions. The development, psychometric properties and normative data of this tool are described in detail in a previous publication (Heggdal et al., 2018). The questionnaire consists of 12 items

scored on a 4-point Likert-scale. Items and scales are scored from 1 (worst) to 4 (best), reflecting how frequently the subject experience difficulties with communication. A mean sum score for all items is generated, as well as sub-scores for listening in quiet and adverse conditions respectively. In addition, a quiet-to-adverse ratio is calculated by dividing the quiet sub-scale score with the adverse sub-scale score. As previous studies have reported equivocal findings regarding the effects of left versus right side HL on reorganization (Heggdal et al., 2016; Eggermont, 2017), we aimed to use this tool to investigate eventual differences between side of hearing loss in self-reported communication ability. Differences between groups were investigated using a one-way ANOVA, with Games-Howell post hoc tests. Quiet and adverse scores were compared in patients using paired samples *t*-tests.

2.4. Stimuli

A "Sound Morphing" paradigm (Specht et al., 2009; Specht et al., 2005; Specht and Wigglesworth, 2018) was utilized. The stimuli consist of white noise, two speech sounds and two music sounds. Speech sounds were consonant-vowel syllables (CV) /da/ and /ta/ read by a male speaker. These speech sounds (subsequently called "phonetic" stimuli) have short and long voice onset times (VOT) respectively and were chosen to control for the differential lateralization effects different VOT may produce (Specht, 2014). In addition, two musical instrument sounds (subsequently called "music" stimuli) were used as non-speech control stimuli. These were a guitar chord and a piano chord (A_3 and C major with a C_3 root respectively). All stimuli lasted 420 ms and were matched in duration and intensity. A third condition consisted of white noise matched in duration and intensity to other stimuli. Through seven parametric steps, phonetic and music sounds were mixed with the white noise, using a morphing procedure with increasingly larger interpolation factors. Thus, the spectral and temporal characteristics of the phonetic and music sound are parametrically emerging from the white noise in seven steps presented in a semi-randomized manner. Subjects were asked to passively listen to these sounds. To ensure that the subjects' attention was relatively constant, they were asked to push a button using their right index finger, when they heard a 1 kHz pure tone. These trials were randomly distributed. The fMRI-experiment lasted for 18 min. Stimuli were presented using MR compatible insulated circumaural headphones. Stimuli and behavioural responses were controlled by E-Prime software (Psychology Software Tools Inc.) running on a computer placed outside of the MR chamber. Intensity of the stimuli was constant and set to 85 dB (A). Levels were measured using a Larson Davis System 824 sound level meter, a Larson Davis PRM902 preamplifier and a Larson Davis AEC101 artificial ear.

Patients with SSD received stimulation to their unaffected ear. Normal hearing controls received binaural stimulation, left-side monaural stimulation or right-side monaural stimulation. Those that received monaural stimulation had the contralateral ear plugged by a single use foam earplug (estimated by the producer to provide 30 dB of attenuation) under the circumaural headphone for the entire scanning session.

2.5. Scanning procedure

MRI scans were performed with a Siemens Prisma 3 T Scanner. Axial slices for the functional imaging were positioned parallel to the AC-PC line using a reference from a high-resolution anatomical brain volume. The anatomical volume was obtained using a T_1-weighted gradient echo pulse sequence. A single session rapid event-related design was utilized for the fMRI experiment, with in total 84 presentations distributed over the 7 manipulation steps of the 2 sound categories (phonetic/music). The design consisted of 168 regular events and 15 target trials with the pure-tone stimuli that required the subjects to push a button. Trials were presented in a pseudo-randomized order, and the averaged inter trial interval for stimuli of the same category and the same manipulation step was 75.2 s [range 3.8–319.2 s]. The averaged inter stimulus interval between any type of stimulation (excluding control trials) was 6.2 s [range 3.8–22.8 s]. Stimulus presentation was triggered by the scanner and happened during a silent gap of 2.3 s between consecutive EPI image acquisitions. Each trial consisted of four stimuli repetitions and lasted 2 s. The fMRI data were acquired with the following parameters: TE 30 ms, TR 3.8 s (comprising of 1.5 s of EPI scanning followed by 2.3 s silent gap for stimulus presentation), 64 × 64 matrix, 26 slices, [3.4 mm × 3.4 mm × 4.4 mm] voxel size, 285 EPI volumes, interleaved acquisition. The subjects were in the scanner for a total of 50 min in a single session.

2.6. Data analysis

Pre-processing and statistical analysis of BOLD-fMRI data was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). First, EPI images were re-aligned and unwarped to adjust for head movement during scanning and to correct for distortions induced by such movement. Realigned EPI images were then coregistered with the high-resolution anatomical scan, which was subsequently normalized to the MNI standard stereotactic space and the corresponding transformation was applied to the realigned EPI images. Finally, the normalized EPI images were smoothed with a Gaussian kernel of 8 mm.

2.7. General linear model analysis

Single subject first level analyses were performed as parametric designs with "phonetic" and "music" as two independent conditions and the seven manipulation steps as parametric factors for each condition. This allows a separation between the general auditory processing of the two conditions and specific responses to the manipulations. The target condition is treated as an independent condition, but no further analysis of this was included in the present study. To capture additional variance, the realignment parameters were included as covariates of no interest. Contrasts were specified for the two conditions (phonetic/music) and for the parametric modulation (para phonetic/para music). Resulting individual contrast images were analysed in second level group analyses. These group analyses were performed as ANOVA models with the factors condition (phonetic/music) as within subject factors, and group as between-subject factor. Corresponding analyses were performed for the specific effects of the manipulations (para phonetic/para music). Post-hoc independent samples *t*-tests were used to compare groups. All analyses reported were corrected for multiple comparisons using a voxel-level threshold of $p < .05$ family-wise-error corrected (FWE).

2.8. Lateralization index

In order to investigate whether hemispheric activity related to the various stimuli conditions and their parametric manipulation was symmetric or lateralized, the "LI-tool" toolbox for SPM was used to calculate a lateralization index (LI) for each condition in each subject (Wilke and Schmithorst, 2006; Wilke and Lidzba, 2007). The implemented temporal mask covering the entire temporal cortices was set as an inclusive mask, and a $+/-$ 5 mm midline exclusion mask was applied. Fig. 1 shows the coverage of the temporal mask used as an inclusive mask for the calculation of the lateralization index. The bootstrapping procedure implemented in the toolbox was used. This calculated 10,000 LIs from 100 bootstrapped resampled voxel values at multiple thresholds in each hemisphere. No clustering or variance weighting was applied. The weighted mean was calculated. Values ranging from -1 to 1 are reported. Negative values suggest right-hemispheric dominance. Positive values suggest a left-hemisphere dominance. Significant lateralization is considered when LI ≥ 0.2 (left) or ≤ -0.2 (right). Other values suggest symmetric hemispheric activity (Wilke and Schmithorst, 2006; Wilke et al., 2006; Norrelgen et al.,

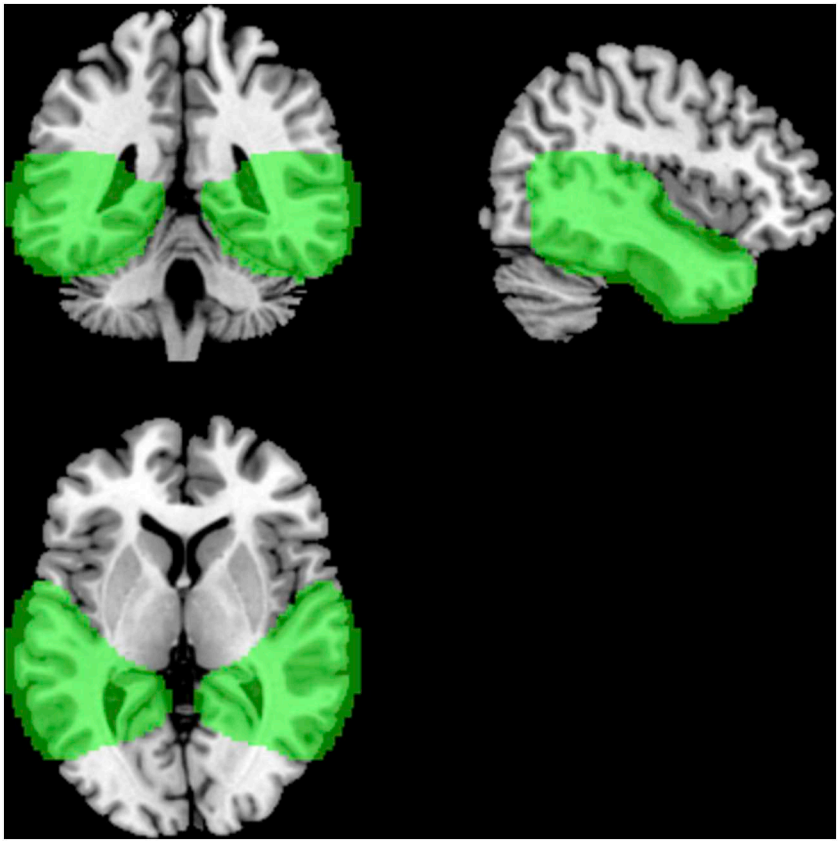

Fig. 1. Coverage of the temporal mask used as an inclusive mask for the calculation of the lateralization index shown in green.

2015) (Evans et al., 2016). This was used to assess between-condition differences within groups of subjects, and between-group differences within conditions. LIs were compared between groups using a one-way ANOVA with Games-Howell post hoc tests. LIs between conditions within groups were compared using paired samples *t*-tests.

3. Results

Activation following phonetic stimuli conditions in normal hearing controls is presented in Table 1. Activation following music stimuli conditions in normal hearing controls is presented in Table 2. Activation following music and phonetic stimuli conditions in patients with SSD is presented in Table 3. Fig. 2 shows activation following phonetic and music stimuli in normal hearing controls. Fig. 3 shows activation following phonetic stimuli in patients with SSD, as well as a comparison between those with left- and right side SSD and correlations to the SAC scores.

3.1. Bilateral stimulation in normal hearing controls

In normal hearing controls, binaurally presented phonetic stimuli and its parametric manipulation yielded bilateral activations in the superior temporal gyrus (STG) corresponding to the auditory cortex on both sides (BA 41). A mean LI of −0.01 (*SD* = 0.45) was found for the phonetic stimuli, while the parametric manipulation of the phonetic stimuli showed a mean LI of 0.03 (*SD* = 0.39).

Similar to the response to phonetic stimuli, binaural music stimuli also produced bilateral activation of the auditory cortex in normal hearing controls. While the right-side activations also included the supramarginal gyrus (BA 40), the left side presented additional activation of an area corresponding to Brodmanns area 22. Thus, activation following binaural music stimuli was not restricted to the auditory cortex, but also involved a left side auditory association area and the right side Inferior parietal lobule. The music stimuli yielded a LI of −0.09 (*SD* = 0.39).

3.2. Monaural stimulation in normal hearing controls

When normal hearing controls received monaural phonetic stimulation of the right ear, bilateral activations of the auditory cortex were seen. In addition, left side activity in the sensory cortex (BA 1) was recorded. A LI of 0.08 (*SD* = 0.49) was recorded. In those receiving monaural phonetic stimulation of the left ear, bilateral auditory cortex was activated, as well as the left side supramarginal gyrus and the right-side premotor cortex. The LI related to this condition was found to be −0.40 (*SD* = 0.33).

The parametric manipulation of the phonetic stimuli in controls that were right side monaurally stimulated activated the auditory cortex bilaterally in addition to a right side activation of an auditory association area. Presented to the left ear, the activity was restricted to bilateral auditory cortex. The para-phonetic condition showed a LI of 0.068 (*SD* = 0.37) when presented to the right ear, and − 0.18 (*SD* = 0.38) when presented to the left ear.

Music stimuli presented monaurally to the right ear in controls activated the auditory cortex on both sides. In addition, left side activation of the primary sensory cortex and right side activation of the supramarginal gyrus was seen. A LI of 0.00 (*SD* = 0.42) was observed. Monaural presentation of music stimuli to the left ear yielded a more complex activation pattern. The supramarginal gyrus and auditory cortices were activated bilaterally, accompanied by left side activation of an area in the fusiform gyrus (BA 37) and right side activity in the primary motor cortex (BA 4) and premotor cortex / supplementary motor cortex (BA 6). The LI for this activation was −0.42 (*SD* = 0.30). For the parametric manipulation of music stimuli, only right side monaural presentation resulted in activity significant after correction. Here, the left side primary sensory cortex and right-side auditory cortex

Table 1
Activation following phonetic stimuli conditions in normal hearing controls. STG: Superior temporal gyrus. PoCG: Post central gyrus. PMC: Premotor cortex. pFWEcorr = *p*-value corrected for family wise error. Ke = Cluster size. Lines printed in bold denote the most significant voxel.

ACTIVATION IN NORMAL HEARING CONTROLS TO PHONETIC STIMULI CONDITIONS

PHONETIC STIMULI

Binaural

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
2146	**< 0.001**	**11.14**	**-36**	**-26**	**10**	**Left**	**STG**	**41**
		10.41	-62	-18	4	Left	STG	41
		10.14	-54	-22	6	Left	STG	41
1679	< 0.001	**9.54**	**38**	**-30**	**16**	**Right**	**STG**	**41**
		8.99	58	-14	6	Right	STG	41
		8.96	40	-24	10	Right	STG	41

Right-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
702	**< 0.001**	**8**	**60**	**-18**	**4**	**Right**	**STG**	**41**
	< 0.001	7.15	50	-12	6	Right	STG	41
	< 0.001	7.91	42	-28	8	Right	STG	41
1083	**< 0.001**	**8**	**-58**	**-16**	**10**	**Left**	**PoCG**	**1**
	< 0.001	6.78	-38	-28	12	Left	STG	41
	< 0.001	6.72	-60	-26	12	Left	STG	41

Left-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
2176	**< 0.001**	**10.35**	**52**	**-12**	**6**	**Right**	**STG**	**41**
		10.17	58	-20	4	Right	STG	41
		8.45	40	-24	12	Right	STG	41
1679	**< 0.001**	**7.98**	**-50**	**-12**	**4**	**Left**	**STG**	**41**
		7.31	-50	-34	20	Left	STG	40
		7.1	-60	-18	4	Left	STG	41
53	**0.005**	**5.74**	**54**	**-8**	**48**	**Right**	**PMC**	**6**

PARAMETRIC MANIPULATION OF PHONETIC STIMULI

Binaural

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
786	**< 0.001**	**11.38**	**-60**	**-20**	**4**	**Left**	**STG**	**41**
514	**< 0.001**	**8.01**	**60**	**-10**	**0**	**Right**	**STG**	**41**
		7.58	54	-18	2	Right	STG	41
		6.34	68	-22	10	Right	STG	41

Right-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
365	**< 0.001**	**8.51**	**-56**	**-18**	**4**	**Left**	**STG**	**41**
238	**< 0.001**	**7.5**	**60**	**-16**	**4**	**Right**	**STG**	**41**
	0.031	5.23	58	-4	-6	Right	STG	22

Left-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
164	**< 0.001**	**6.95**	**-60**	**-14**	**2**	**Left**	**STG**	**41**
180	**< 0.001**	**6.32**	**58**	**-20**	**4**	**Right**	**STG**	**41**
	0.006	5.73	66	-22	8	Right	STG	41
	0.01	5.59	62	-8	2	Right	STG	41

Table 2
Activation following music stimuli conditions in normal hearing controls. STG: Superior temporal gyrus. PoCG: Post central gyrus. PMC: Premotor cortex. FFG: Fusiform Gyrus. SMA: Supplementary motor area. pFWEcorr = p-value corrected for family wise error. Ke = Cluster size. Lines in bold denote the most significant voxel.

ACTIVATION IN NORMAL HEARING CONTROLS TO MUSIC STIMULI CONDITIONS

MUSIC STIMULI

Binaural

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
1674	**< 0.001**	**10.87**	**-38**	**-26**	**10**	**Left**	**STG**	**41**
		10.32	-46	-16	4	Left	STG	41
		8.17	-62	-20	4	Left	STG	22
1425	**< 0.001**	**9.66**	**40**	**-32**	**16**	**Right**	**STG**	**40**
		9.15	40	-22	8	Right	STG	41
		7.79	50	-12	6	Right	STG	41

Right-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
814	**< 0.001**	**7.65**	**-48**	**-14**	**6**	**Left**	**STG**	**41**
		7.07	-38	-28	14	Left	STG	41
		6.9	-58	-14	12	Left	PoCG	1
455	**< 0.001**	**7.38**	**50**	**-10**	**8**	**Right**	**STG**	**41**
		6.49	42	-28	6	Right	STG	41
		6.2	40	-32	16	Right	STG	40

Left-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
1586	**< 0.001**	**8.59**	**52**	**-10**	**6**	**Right**	**STG**	**41**
		8.35	40	-30	18	Right	STG	40
		7.38	40	-22	8	Right	STG	41
271	**< 0.001**	**6.89**	**-36**	**-34**	**18**	**Left**	**STG**	**40**
		6.78	-50	-36	20	Left	STG	40
91	**0.001**	**6.71**	**-48**	**-12**	**2**	**Left**	**STG**	**41**
16	**0.005**	**5.4**	**-30**	**-50**	**-18**	**Left**	**FFG**	**37**
28	**0.002**	**5.34**	**42**	**-16**	**52**	**Right**	**PMC**	**4**
		5.29	50	-10	52	**Right**	**SMA**	**6**

PARAMETRIC MANIPULATION OF MUSIC STIMULI

Right-side stimulation

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
92	**< 0.001**	**6.46**	**-58**	**-16**	**8**	**Left**	**PoCG**	**1**
19	**0.004**	**5.77**	**62**	**-14**	**4**	**Right**	**STG**	**41**
12	**0.007**	**5.5**	**54**	**-8**	**4**	**Right**	**STG**	**41**

Table 3
Activation following phonetic and music stimuli conditions in patients. STG: Superior temporal gyrus. PoCG: Post central gyrus. PMC: Premotorcortex. Ke = cluster size. Lines printed in bold denote the most significant voxel.

ACTIVATION IN PATIENTS TO PHONETIC STIMULI CONDITIONS

PHONETIC STIMULI

Right-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
398	**< 0.001**	**7.35**	**62**	**-18**	**2**	**Right**	**STG**	**22**
	< 0.001	6.42	54	-12	4	Right	STG	41
	0.001	6.24	64	-26	6	Right	STG	41
63	**0.005**	**5.76**	**-62**	**-20**	**4**	**Left**	**STG**	**22**

Left-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
830	**< 0.001**	**8.26**	**-38**	**-28**	**14**	**Left**	**STG**	**41**
	< 0.001	7.61	-58	-28	10	Left	STG	41
	< 0.001	7.59	-56	-16	10	Left	PoCG	1
71	**0.002**	**6.03**	**60**	**-20**	**4**	**Right**	**STG**	**41**
17	**0.01**	**5.53**	**48**	**-10**	**4**	**Right**	**STG**	**41**

PARAMETRIC MANIPULATION OF PHONETIC STIMULI

Right-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
515	**< 0.001**	**8.96**	**-56**	**-10**	**0**	**Left**	**STG**	**22**
	0.013	5.49	-64	-30	4	Left	STG	21
375	**< 0.001**	**7.76**	**60**	**-6**	**2**	**Right**	**STG**	**41**
	< 0.001	7.63	62	-18	2	Right	STG	22
	< 0.001	6.48	62	0	-6	Right	STG	22

Left-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
455	**< 0.001**	**8.59**	**-60**	**-20**	**4**	**Left**	**STG**	**41**
	< 0.001	7.33	-58	-10	0	Left	STG	22
	< 0.001	6.56	-58	-26	-2	Left	STG	22
670	**< 0.001**	**7.01**	**60**	**-6**	**4**	**Right**	**STG**	**41**
	< 0.001	6.88	56	-14	7	Right	STG	41
	< 0.001	6.38	62	-16	0	Right	STG	22

ACTIVATION IN PATIENTS TO MUSIC STIMULI CONDITIONS

MUSIC STIMULI

Right-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
19	**0.004**	**5.69**	**52**	**-10**	**4**	**Right**	**STG**	**41**
12	0.008	5.52	54	-28	10	Right	STG	41

Left-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
487	**< 0.001**	**7.27**	**-36**	**-28**	**14**	**Left**	**STG**	**41**
		7.16	-46	-14	4	Left	STG	41
		6.36	-58	-28	10	Left	STG	41
21	**0.003**	**5.56**	**48**	**-8**	**4**	**Right**	**STG**	**41**

PARAMETRIC MANIPULATION OF MUSIC STIMULI

Right-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
13	**0.007**	**5.54**	**-54**	**-12**	**2**	**Left**	**STG**	**41**
	0.003	5.47	62	-8	2	Right	STG	41

Left-side deafness

Statistical values			Coordinates			Anatomical location		
Cluster level		Peak-level						
Ke	pFWEcorr	*T*	*x*	*y*	*z*	Hemisphere	Structure	BA
17	**0.004**	**5.84**	**-58**	**-18**	**8**	**Left**	**PoCG**	**1**

was activated, and the LI was found to be 0.00 (*SD* = 0.39).

3.3. Monaural stimulation in patients with SSD

When the unaffected left ear in patients with right-side deafness received phonetic stimuli, bilateral activation of an area corresponding to Wernicke's area (BA 22) was seen. In the right STG, activation of the auditory cortex was also seen. LI was −0.33 (*SD* = 0.32). In patients with left-side deafness, phonetic stimulation of the unaffected right side activated bilateral auditory cortex and the left-side primary sensory cortex and produced a LI of 0.2 (*SD* = 0.48).

In patients with right-side deafness, for the parametric manipulation of phonetic stimuli, bilateral activation of BA 22 was seen. This condition also activated right-side auditory cortex in addition to an area in the temporal cortex (BA 21) on the left side. In patients with left-side deafness, the parametric manipulation involved the auditory cortex and BA 22 bilaterally. The LI for the parametric manipulated phonetic condition was −0.12 (*SD* = 0.36) in those with right-side deafness and − 0.05 (*SD* = 0.51) in those with left-side deafness.

Music stimuli presented to the unaffected left ear in patients with right-side deafness yielded activity in the right-side auditory cortex with a LI of −0.27 (*SD* = 0.39). Following parametric manipulation of music stimulation, the auditory cortex was activated bilaterally and showed a LI of −0.2 (*SD* = 0.45). Those with left-side deafness, receiving monaural music stimulation of the right ear showed bilateral activation of the auditory cortex LI of 0.03 (*SD* = 0.52), while the parametric condition only activated the left side primary sensory cortex and yielded a LI of −0.2 (*SD* = 0.49).

3.4. Differences in activations between groups

Following FWE-correction for multiple comparisons, no differences were seen for any stimuli condition when comparing patients to any control group. No differences were seen between controls receiving monaural or binaural stimuli.

When response to auditory stimuli in patients with right and left side deafness was compared, those with right side deafness showed some right-side activity not seen in patients with left side deafness for the phonetic stimuli condition. This activity was seen in the frontal cortex (FC) (BAs 8, & 47) and the posterior part of the insular cortex (IC) (BA 13) (Table 4).

3.5. Differences in lateralization between groups

Table 5 shows LIs in groups of subjects (grouped by ear stimulated) for the different stimuli conditions. To assess differences in lateralization between groups, one-way ANOVAs were conducted using stimuli conditions as dependent values and groups of subjects as the factor. For the parametric manipulation of phonetic stimuli ($F(4,69) = 0.873$, $p = .49$) and the parametric manipulation of music conditions ($F(4,59) = 0.662$, $p = .621$) there were no statistically significant differences between groups. For the phonetic stimuli ($F(4,59) = 4.07$, $p = .006$) and music stimuli ($F(4,59) = 2.60$, $p = .046$) there were statistically significant differences between groups.

This was followed by Games-Howell post hoc tests which revealed that for the phonetic condition, controls receiving left-side monaural stimulation had significantly more right-lateralized activations than patients (-0.59 ± 0.18, $p = .03$) receiving right-side monaural stimulation. For the music condition, no between-groups differences were found to be statistically significant following the Games-Howell post hoc test.

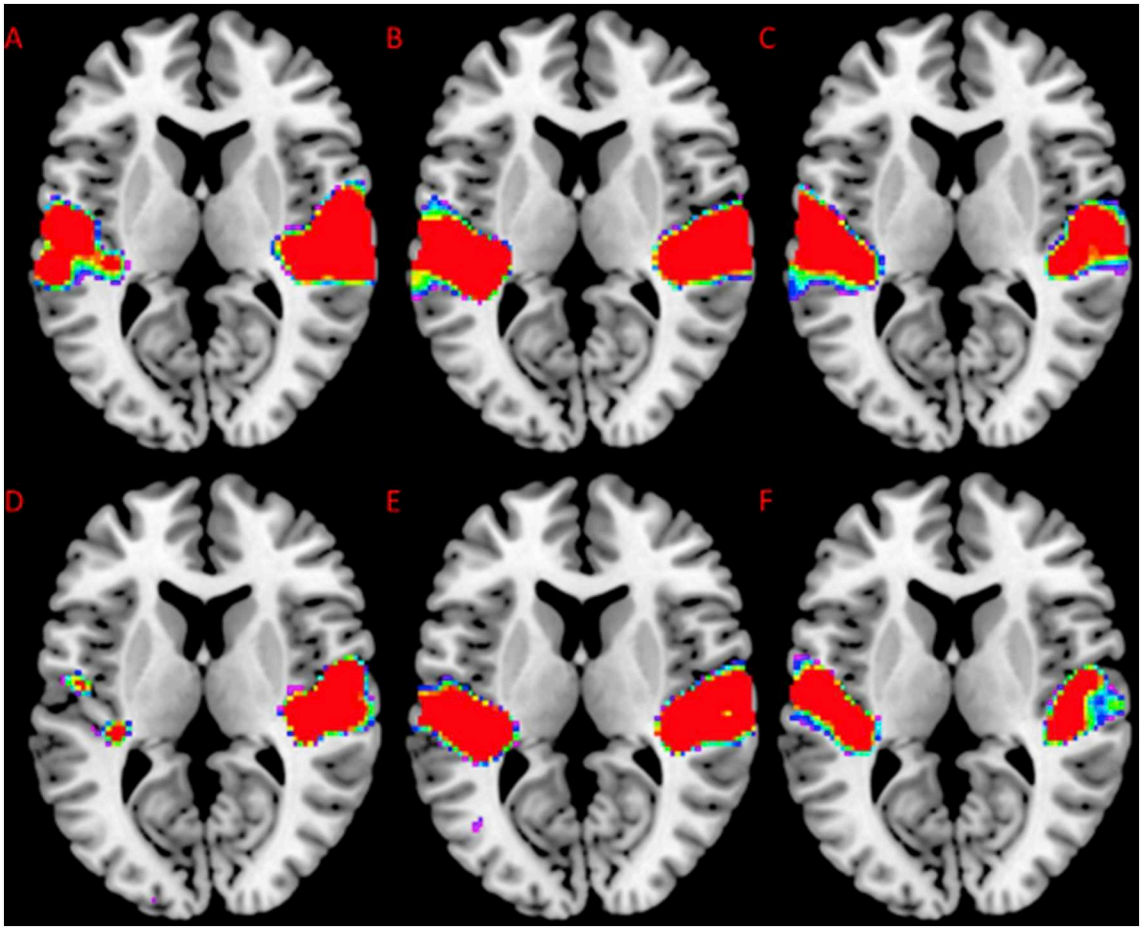

Fig. 2. All results are FWE, p < .05, > 10 voxels. A, B and C shows activation following left (n = 14) bilateral (n = 21) and right (n = 15) phonetic stimuli in normal hearing controls. D, E and F shows activation in the same groups of subjects following music stimuli.

3.6. Differences in lateralization within groups

In normal hearing controls, no significant difference was seen in lateralization between phonetic stimuli and parametric manipulation of phonetic stimuli in those receiving binaural or right side stimulation, when performing paired-sample t-tests within stimulation groups ($p > .05$). In those controls that received monaural stimulation of the left ear, significantly more right-lateralized activation was seen for the phonetic condition compared to the parametric manipulation in the phonetic condition (-0.21 ± 0.32, $p < .05$). Similar analyses were then made for music and phonetic stimuli, music and parametric manipulation of music stimuli and for the manipulated music and manipulated phonetic stimuli within each group of controls. A significant difference in lateralization was discovered between music and the parametric manipulation of music stimuli in controls receiving left side stimulation, where the music condition was more right lateralized (-0.37 ± 0.66, $p < .05$).

The same between-conditions comparisons of lateralization were performed within the two patient groups. In those with right-side SSD, no significant differences were observed between phonetic / "para" phonetic, music / "para" music, phonetic / music stimulation conditions ($p > .05$). In those with left-side SSD, a significant difference was seen between phonetic and parametric manipulation of phonetic stimulation, where the phonetic stimuli yielded more left-lateralized activation as compared to the symmetric activity following parametric manipulation of phonetic stimuli (0.25 ± 0.32, $p < .05$).

3.7. Self-assessment of communication (SAC)

Table 6 presents mean scores (SD) in groups of participants for total scale, subscales "Quiet" and "Adverse" and the quiet / adverse ratio. A one-way multivariate analysis of variance (ANOVA) was run to determine the effect of group (control, right side or left side SSD) on the SAC-questionnaire scores. Total scale score ($F(2, 62) = 123.14$, $p < .001$), subscale quiet ($F(2, 62) = 49.6$, $p < .000$), subscale adverse ($F(2, 62) = 149.41$, $p < .001$) and quiet-to-adverse ratio ($F(2, 62) = 67.75$, $p < .000$) differed significantly between groups. As groups were unequal in size, the equality of means was assessed using the Welch test. Means were not equal between groups. Thus, differences between groups were investigated in follow-up ANOVAs using Games-Howell post-hoc tests. Controls had significantly ($p < .001$) better scores in all measures than both patient groups. No significant ($p > .05$) differences were seen in sum score, subscale scores or quiet-to-adverse ratio between patient groups.

When developing the questionnaire we suggested a cut-off score for normal hearing subjects at 3.2 points (Heggdal et al., 2018). As seen in Table 6, patients with SSD score similar to this for the quiet sub-scale, suggesting performance at a normal hearing level, while the score for the adverse sub-scale is poorer. A paired samples t-test was performed to compare quiet- and adverse scores in patients. This revealed a significant difference in the scores for the two conditions ($t(20) = 12.31$, $p = .006$). Thus, the questionnaire seems to detect difficulties experienced by patients with SSD in adverse listening scenarios.

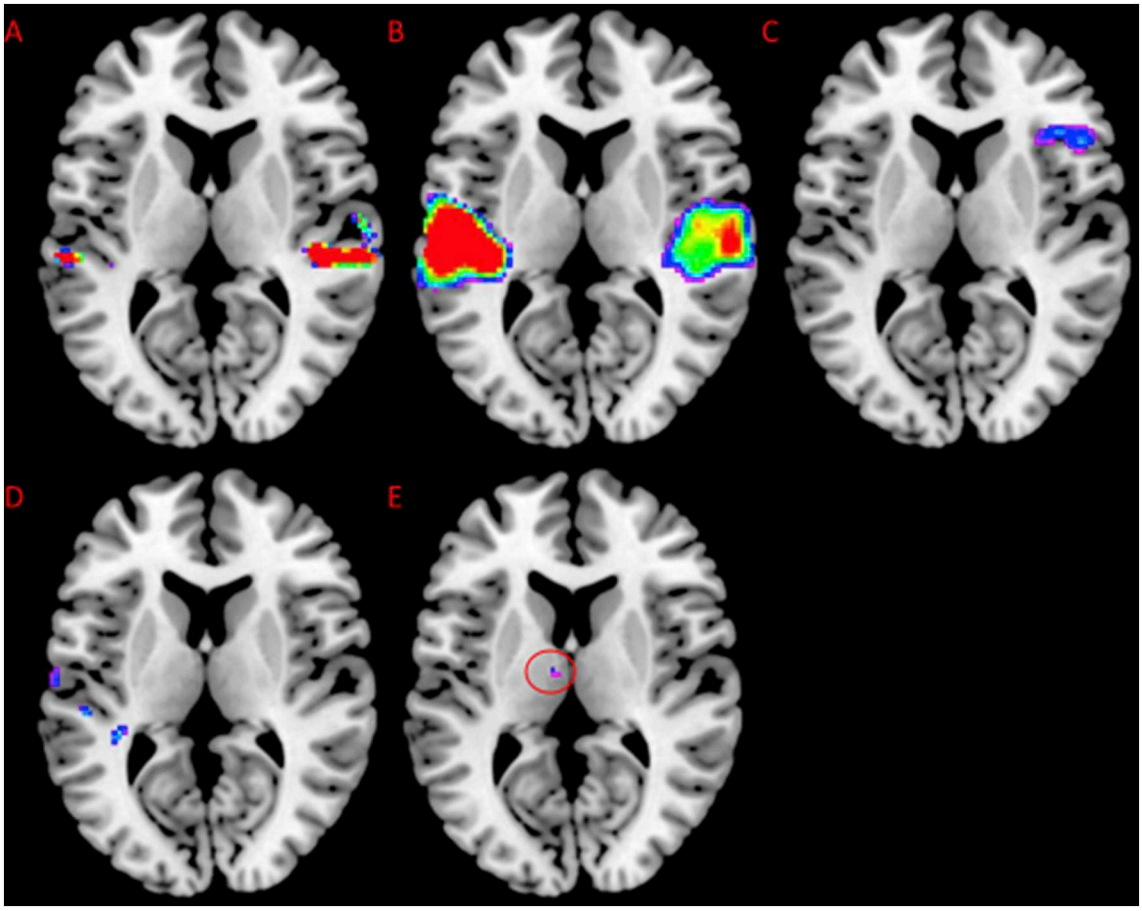

Fig. 3. All results are FWE, p < .05, > 10 voxels. **A** and **B** shows activation following phonetic stimuli in those with right (n = 12) and left (n = 10) SSD. **C** shows a comparison of activity in the two patient groups (Right SSD – Left SSD). **D** shows the correlation between activity following phonetic stimuli and the mean sum score for the SAC in all patients. **E** shows the correlation between the quiet / adverse ratio from the SAC and activity following phonetic stimuli.

Table 4
Areas that show increased activity in right SSD compared to left SSD in response to phonetic stimuli. Lines printed in bold denote the most significant voxel.

Right side SSD vs Left side SSD: Phonetic stimuli									
Statistical values				Coordinates			Anatomical location		
Cluster level		Peak-level		*x*	*y*	*z*	Hemisphere	Structure	BA
Ke	pFWEcorr	*T*	*Puncorr*						
3	**0.025**	**5.35**	**0**	**48**	**22**	**−4**	**Right**	**FC**	**47**
5	**0.019**	**5.26**	**0**	**34**	**22**	**−6**	**Right**	**IC**	**13**
6	**0.016**	**5.2**	**0**	**42**	**22**	**4**	**Right**	**FC**	**45**
3	**0.025**	**5.12**	**0**	**2**	**22**	**52**	**Right**	**FC**	**8**

FC: Frontal cortex.
IC: Insular cortex.
Ke = Cluster size.

3.8. Correlations to self-reported communication in patients

A multiple regression analysis was made, where scores from the questionnaire were entered as vectors in a covariate to the BOLD-response to auditory stimuli. In patients with SSD, the total scale score correlated positively to activity following phonetic stimuli in two regions, the left auditory cortex ($^{k}_{E}$ 7, T = 5.92 [MNI -44, −30, 4]) and the left primary sensory cortex ($^{k}_{E}$ 2, T = 5.59 [MNI -58, −20, 18]). Also, an inverse correlation was found between the quiet / adverse ratio and activity in the left thalamus ($^{k}_{E}$ 4, T = 5.51 [MNI -6, −18, 16]). No such correlations were seen for the parametric manipulation of phonetic stimuli or to any of the music conditions. In normal hearing controls, no correlations between BOLD-responses to any stimuli condition and questionnaire scores were found.

3.9. Correlations to hearing loss duration

A multiple regression analysis was made, where the duration of hearing loss was entered as a vector in a covariate to the BOLD-response to auditory stimuli. No correlations were seen for any stimuli condition and the duration of hearing loss in those with SSD.

4. Discussion

The side of stimulation and the type of stimuli affects hemispheric balance in persons with normal hearing and persons with SSD. Monaurally delivered auditory stimuli yielded bilateral activations in our normal hearing controls. This is partly in contrast to several previous studies using e.g. sine tones and random spectrographic sounds as stimuli ((Scheffler et al., 1998; Burton et al., 2012)), where the activations were more strongly lateralized than in the present study. Bilateral activation in normal hearing controls following monaural stimulation was seen for both phonetic and music stimuli in the present study. Thus, the discrepancies in lateralization between past and present results could at least in part be due to the type of stimuli applied. Except for the parametric manipulation of music stimulation in the right ear, all conditions activated bilateral auditory cortices. LIs for monaural right side stimulation in controls show symmetric activity, while left side stimulation shows contralateral dominance for phonetic

Table 5
Descriptive information for lateralization indexes for groups of subjects and stimuli conditions. Groups formed by ear stimulated.

Lateralization for stimuli conditions in groups of subjects					
Group (Ear stimulated)	*M*	*SD*	*Min*	*Max*	*Lateralization*
Bilateral control (n = 19)					
Phonetic	−0.01	0.45	−0.65	0.69	–
Para Phonetic	0.03	0.39	−0.70	0.58	–
Music	−0.09	0.40	−0.72	0.70	–
Para Music	−0.15	0.42	−0.73	0.50	–
Left-side Control (n = 14)					
Phonetic	−0.40	0.33	−0.69	0.57	→
Para Phonetic	−0.18	0.38	−0.70	0.77	–
Music	−0.42	0.30	−0.75	0.27	→
Para Music	−0.05	0.39	−0.62	0.66	–
Right-side control (n = 15)					
Phonetic	0.08	0.49	−0.74	0.75	–
Para Phonetic	0.07	0.37	−0.44	0.58	–
Music	0.00	0.40	−0.91	0.58	–
Para Music	0.00	0.39	−0.69	0.82	–
Left-side patient (n = 12)					
Phonetic	−0.33	0.33	−0.74	0.22	→
Para Phonetic	−0.12	0.36	−0.61	0.36	–
Music	−0.27	0.39	−0.77	0.32	→
Para Music	−0.21	0.45	−0.82	0.53	→
Right-side patient (n = 10)					
Phonetic	0.20	0.48	−0.66	0.69	←
Para Phonetic	−0.05	0.51	−0.95	0.52	–
Music	0.03	0.52	−0.85	0.69	–
Para Music	−0.20	0.49	−0.87	0.55	→

— = Mean LI is symmetric.
→ = Mean LI is right-lateralized.
← = Mean LI is left-lateralized.
Para: parametric manipulation.

Table 6
Mean scores (*SD*) in groups of participants. For total scale and subscales "Quiet" and "Adverse".

	Group		
Scores	*RSSD (n = 12)*	*LSSD (n = 10)*	*Controls (n = 50)*
Total scale	2.52 (0.49)	2.75 (0.48)	3.81 (0.20)
Quiet	3.17 (0.52)	3.24 (0.47)	3.92 (0.10)
Adverse	1.62 (0.60)	2.06 (0.60)	3.64 (0.38)
Quiet/Adverse ratio	2.14 (0.65)	1.66 (0.35)	1.09 (0.12)

RSSD: Right-side single-sided deafness.
LSSD: Left-side single-sided deafness.

and music stimuli.

Considering previous reports of contralateral lateralization in normal hearing persons, the balanced response in controls that received right-side monaural stimuli could also be the result of an immediate plastic process motivated by plugging one ear for a period of ~ 30 min. This could motivate an increase of ipsilaterally projected information from the brainstem to the central auditory pathways, usually reported as inhibited when both ears are receiving auditory stimuli (Pross et al., 2015; Chang et al., 2016; Kaneko et al., 2003; Brancucci et al., 2004). If such short-term deprivation of peripheral auditory input alters the hemispheric workload distribution in normal hearing controls, this implies that the neuronal network for auditory perception is very responsive to peripheral changes. Also, it suggests that the cortical activations seen in studies of auditory perception is the result of a highly dynamic, ongoing process, that is affected by both the long-term and the short-term balance of input from the two peripherals. Possibly, even a period of ~30 min of monaural deprivation will motivate a functional reorganization to optimize the processing of auditory stimuli. The different LIs between left- and right-side monaural stimulation in our controls also show that studies on lateralization should be aware that various stimuli types would yield different results. Thus, right- and left ears should not be pooled when analyzing results.

Patients with right side SSD showed more activations of some frontal cortical areas than patients with left side SSD following phonetic stimuli. This might be related to a higher level of effort in these patients. While we found no significant differences in SAC-scores between patient groups (when correcting for multiple comparisons), a trend was observed for the subscale "adverse listening conditions" with worse scores in those with right side SSD (p = .09). Also, those with right side SSD showed a trend towards a worse quiet/adverse ratio when compared to those with left side SSD (p = .047), possibly suggesting that those with right side SSD are more affected by background noise. Regions of the frontal cortex have been shown to be involved in extracting meaning from degraded speech signals. Possibly, right side SSD, to a larger extent than left side SSD, cause non-degraded phonetic stimuli to require resources normally needed for the processing of degraded stimuli (Peelle, 2018). These aspects should be investigated further in future studies, by implementing measures of listening effort. While in children, a relevant finding in this context was reported by Propst et al., (2010). They found that those with right side SSD failed to activate some auditory association areas when listening to speech in noise. Normal hearing children, and those with left side SSD activated such areas listening to the same stimuli. Also, those with left side SSD also showed activity in bilateral visual association areas during the same task, while this did not occur in those with right side SSD. Differences between those with left and right SSD has also been reported in earlier studies investigating long latency auditory evoked potentials (AEPs). Hanss et al. (2009) found that when listening to non-speech sounds, those with left side hearing loss showed symmetrical activation patterns, similar to that of a binaural stimulation in their normal hearing subjects. These changes, seen both for amplitudes and time course of the AEPs were however not present in those with right side hearing loss.

Controls receiving right-side stimulation showed symmetric hemispheric workload for all stimuli conditions. Patients with left-side SSD, thus receiving the same right-side monaural stimulation on the other hand, showed symmetric responses to the parametric manipulation of phonetic stimuli and music stimuli, while the phonetic and parametric manipulation of music stimuli yielded left and right side hemispheric dominance respectively. This supports our hypothesis that stimuli content and complexity affect the right- and left-side hemispheric involvement in auditory processing and reorganization following SSD. Also, this is in line with previous studies that have suggested that left side SSD will motivate the plastic process to a larger extent than right side SSD (Hanss et al., 2009; Heggdal et al., 2016; Eggermont, 2017; Propst et al., 2010).

In those with SSD, stronger activity in the left auditory cortex and the left primary sensory cortex following phonetic stimuli was associated to better outcome in the SAC sum-score. This, and the inverse correlation observed between the quiet / adverse ratio and activation of an area in the left thalamus suggests that degree of activation in these areas is related to better self-reported communication ability. This is in line with current theories on speech perception (see e.g. (Specht, 2014)). As the quiet / adverse ratio reflects the relative difficulty experienced when listening to speech in noise as compared to speech in quiet scenarios, this suggests a role of the thalamus in processing of degraded speech / performance in adverse listening conditions in persons with SSD. The existence of a cerebellar-thalamic network for speech perception has been suggested previously (Muller et al., 1998), and Salvi et al. (2002) reported increased thalamic activity when processing speech in noise compared to speech in quiet. They also reported that an even larger activation was seen when subjects had to remember and repeat the last word presented in the presence of noise, thus suggesting a relationship between thalamic activation and listening effort. Hence, we suggest that the correlations between thalamic activity and

SAC-scores are related to the problems faced by persons with SSD when processing speech in noise, and their activation of a cerebellar-thalamic network for speech perception in adverse condition.

The discrepancy in activity lateralization between the present and previous results may be due to the spectral-temporal complexity of the stimuli we used, opposed to the less complex stimuli used in previous studies. For example, Scheffler et al. (1998) reported a strong contralateral lateralization of the cortical response to monaural stimulation using pure tones in normal hearing controls, while those with SSD had much more balanced responses, more similar to a binaural stimulation of the normal hearing subjects. A similar finding was made by Schmithorst et al. (2005) in a study that included children aged 7–12 years with unilateral hearing loss. Using pure tones with randomized durations and frequencies, they found a balanced response of both sides' auditory cortex. It was not always reported in previous studies whether or not subjects receiving monaural stimuli had the opposite ear plugged or not. Furthermore, the numbers of subjects were relatively low in previous studies. It should also be noted that previous studies included few patients. While Scheffler et al. (1998) and Schmithorst et al. (2005) included five and eight patients respectively; Bilecen et al. (2000) and Firszt et al. (2013) both were single-subject studies. Considering the considerable variation we observed in lateralization between subjects, both patients and controls, this could affect the ability to conclude on the matter of lateralization of monaural stimulation in both patients and controls in small cohorts (including that of the present study). As seen in Table 5, in all groups and for all stimuli, there are considerable inter-subject variations in lateralization. Even in normal hearing controls receiving binaural stimulation, both strong left- and right-side lateralization is seen for all stimuli types in single subjects. This is a limitation in the present study as well, where an even larger number of patients would be desirable. Nevertheless, as suggested by Pross et al. (2015), we focused on including patients that were well controlled for etiology, hearing loss configuration and hearing loss duration, at the expense of a higher sample size.

As expected from previous reports (Gatehouse and Speech, 2004) (Pross et al., 2015), results from the questionnaire on self-assessment of communication ability in quiet and adverse listening scenarios (SAC) show that persons with SSD are faced with a varying level of difficulty across listening scenarios. While they report a low level of difficulty in quiet listening scenarios, they frequently experience problems in adverse situations. Compared to normative data (Heggdal et al., 2018), persons with SSD score similar to normal hearing persons in quiet scenarios and similar to those with severe to profound HL in adverse listening scenarios. We suggest that this could contribute to the reduced quality of life seen in previous studies of persons with VS (Myrseth et al., 2005; Myrseth et al., 2006a; Myrseth et al., 2006b), due to the variation in difficulties across situations they may face during the day, as opposed to the more constant level of difficulty in persons with bilateral hearing loss. This would however need to be investigated more directly using measures of both generic and specific quality of life in this group.

We were not able to detect differences between patients and controls after FWE correction. There are several possible explanations for this. Despite that all subjects wore noise-insulating headphones, the noise from the scanner could influence the results of our study. However, this would likely affect all groups equally, and would also have been the case in previous similar studies. Also, the level of the stimuli used in the present study could cause cross-listening, where stimuli travels across the scull to reach the contralateral ear, preventing true monaural stimulation. It could also be that differences between patients and controls occur within a time frame that is too short to be detected by fMRI. The temporal resolution of fMRI is limited by the relatively slow BOLD-response, as its peak occurs 5–6 s after brief neural stimulation, which is much slower than the underlying neural processes that we are indirectly measuring (Glover, 2011). Thus, there could be differences in the processing of monaural and binaural auditory stimuli, and between stimuli conditions, that we are not able to detect with the current experiment. Here, the superior temporal resolution of electrophysiological methods could be of value in future studies. Another possible limitation of our study could be that the stimuli were not sufficiently complex to reveal the consequences of long-term monaural deprivation. Possibly, patients and controls process these relatively simple stimuli more similarly than what would be the case for sentences or for spoken words in noise, for example.

5. Conclusion

In both persons with SSD and normal hearing controls, hemispheric dominance following monaural auditory stimulation is modulated by the spectral-temporal properties of the stimuli and by which ear is stimulated. Overall, the BOLD-response in patients is similar to that of normal hearing controls. Possibly, this could be due to the duration of hearing loss in our subjects (at least two years). Future studies could aim to investigate the BOLD-response in patients closer to hearing loss onset. Also, the fMRI-experiment could fail to reveal actual differences due to its limited temporal resolution. Including measures of auditory evoked potentials (AEPs) could provide information on the most immediate neural activity following auditory stimuli in those with SSD. Differences in the BOLD-response to phonetic stimuli and in its correlations to the SAC-scores observed between patients with right- and left side SSD suggests that right side SSD is related to increased activation of areas usually related to processing of degraded input.

Declaration of Competing Interest

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

References

Anne, S., Lieu, J.E.C., Cohen, M.S., 2017. Speech and language consequences of unilateral hearing loss: a systematic review. Otolaryngol. Head Neck Surg. 157 (4), 572–579. Epub 2017/08/23. https://doi.org/10.1177/0194599817726326 (PubMed PMID: 28828919).

Annett, M., 1970. A classification of hand preference by association analysis. Br. J. Psychol. 61 (3), 303–321 Epub 1970/08/01. (PubMed PMID: 5457503).

Bilecen, D., Seifritz, E., Radu, E.W., Schmid, N., Wetzel, S., Probst, R., et al., 2000. Cortical reorganization after acute unilateral hearing loss traced by fMRI. Neurology. 54 (3), 765–767 (Epub 2000/02/19. PubMed PMID: 10680824).

Brancucci, A., Babiloni, C., Babiloni, F., Galderisi, S., Mucci, A., Tecchio, F., et al., 2004. Inhibition of auditory cortical responses to ipsilateral stimuli during dichotic listening: evidence from magnetoencephalography. Eur. J. Neurosci. 19 (8), 2329–2336. Epub 2004/04/20. https://doi.org/10.1111/j.0953-816X.2004.03302.x (PubMed PMID: 15090059).

Burton, H., Firszt, J.B., Holden, T., Agato, A., Uchanski, R.M., 2012. Activation lateralization in human core, belt, and parabelt auditory fields with unilateral deafness compared to normal hearing. Brain Res. 1454, 33–47. Epub 2012/04/17. https://doi.org/10.1016/j.brainres.2012.02.066 (PubMed PMID: 22502976; PubMed Central PMCID: PMCPMC3403813).

Burton, H., Firszt, J.B., Holden, T., 2013. Hearing thresholds and FMRI of auditory cortex following eighth cranial nerve surgery. Otolaryngol. Head Neck Surg. 149 (3), 492–499. Epub 2013/06/28. https://doi.org/10.1177/0194599813495179 (PubMed PMID: 23804630; PubMed Central PMCID: PMCPMC3836431).

Chang, J.L., Pross, S.E., Findlay, A.M., Mizuiri, D., Henderson-Sabes, J., Garrett, C., et al., 2016. Spatial plasticity of the auditory cortex in single-sided deafness. Laryngoscope. 126 (12), 2785–2791. Epub 2016/03/10. https://doi.org/10.1002/lary.25961 (PubMed PMID: 26951886).

Eggermont, J.J., 2017. Acquired hearing loss and brain plasticity. Hear. Res. 343, 176–190. Epub 2016/05/29. https://doi.org/10.1016/j.heares.2016.05.008 (PubMed PMID: 27233916).

Evans, S., McGettigan, C., Agnew, Z.K., Rosen, S., Scott, S.K., 2016. Getting the cocktail party started: masking effects in speech perception. J. Cogn. Neurosci. 28 (3), 483–500. Epub 2015/12/24. https://doi.org/10.1162/jocn_a_00913 (PubMed PMID: 26696297; PubMed Central PMCID: PMCPMC4905511).

Firszt, J.B., Reeder, R.M., Holden, T.A., Burton, H., Chole, R.A., 2013. Changes in auditory perceptions and cortex resulting from hearing recovery after extended congenital unilateral hearing loss. Front. Syst. Neurosci. 7 (108). https://doi.org/10.3389/fnsys.2013.00108. Epub 2014/01/01. (PubMed PMID: 24379761; PubMed Central PMCID: PMCPMC3861790).

Gatehouse, S., Speech, Noble W. The, 2004. Spatial and Qualities of Hearing Scale (SSQ). Int. J. Audiol. 43 (2), 85–99 Epub 2004/03/24. (PubMed PMID: 15035561; PubMed

Central PMCID: PMCPMC5593096).
Glover, G.H., 2011. Overview of functional magnetic resonance imaging. Neurosurg. Clin. N. Am. 22 (2), 133–139. vii. Epub 2011/03/26. https://doi.org/10.1016/j.nec.2010.11.001 (PubMed PMID: 21435566; PubMed Central PMCID: PMCPMC3073717).
Hanss, J., Veuillet, E., Adjout, K., Besle, J., Collet, L., Thai-Van, H., 2009. The effect of long-term unilateral deafness on the activation pattern in the auditory cortices of French-native speakers: influence of deafness side. BMC Neurosci. 10 (23). https://doi.org/10.1186/1471-2202-10-23. Epub 2009/03/25. (PubMed PMID: 19309511; PubMed Central PMCID: PMCPMC2662863).
Harkonen, K., Kivekas, I., Rautiainen, M., Kotti, V., Vasama, J.P., 2017. Quality of life and hearing eight years after sudden sensorineural hearing loss. Laryngoscope. 127 (4), 927–931. Epub 2016/06/22. https://doi.org/10.1002/lary.26133 (PubMed PMID: 27328455).
Heggdal, P.O.L., Brannstrom, J., Aarstad, H.J., Vassbotn, F.S., Specht, K., 2016. Functional-structural reorganisation of the neuronal network for auditory perception in subjects with unilateral hearing loss: review of neuroimaging studies. Hear. Res. 332, 73–79. Epub 2015/12/29. https://doi.org/10.1016/j.heares.2015.11.015 (PubMed PMID: 26707432).
Heggdal, P.O.L., Nordvik, O., Brannstrom, J., Vassbotn, F., Aarstad, A.K., Aarstad, H.J., 2018. Clinical application and psychometric properties of a norwegian questionnaire for the self-assessment of communication in quiet and adverse conditions using two revised aphab subscales. J. Am. Acad. Audiol. 29 (1), 25–34. Epub 2018/01/09. https://doi.org/10.3766/jaaa.16102 (PubMed PMID: 29309021).
Kaneko, K., Fujiki, N., Hari, R., 2003. Binaural interaction in the human auditory cortex revealed by neuromagnetic frequency tagging: no effect of stimulus intensity. Hear. Res. 183 (1-2), 1–6 Epub 2003/09/19. (PubMed PMID: 13679132).
Khosla, D., Ponton, C.W., Eggermont, J.J., Kwong, B., Don, M., Vasama, J.P., 2003. Differential ear effects of profound unilateral deafness on the adult human central auditory system. J. Assoc. Res. Otolaryngol. 4 (2), 235–249. Epub 2003/08/29. https://doi.org/10.1007/s10162-002-3014-x (PubMed PMID: 12943375; PubMed Central PMCID: PMCPMC3202721).
Lewis, D., Schmid, K., O'Leary, S., Spalding, J., Heinrichs-Graham, E., High, R., 2016. Effects of noise on speech recognition and listening effort in children with normal hearing and children with mild bilateral or unilateral hearing loss. J Speech Lang Hear Res. 59 (5), 1218–1232. Epub 2016/10/30. https://doi.org/10.1044/2016_JSLHR-H-15-0207 (PubMed PMID: 27784030; PubMed Central PMCID: PMCPMC5345560).
Muller, R.A., Chugani, D.C., Behen, M.E., Rothermel, R.D., Muzik, O., Chakraborty, P.K., et al., 1998. Impairment of dentato-thalamo-cortical pathway in autistic men: language activation data from positron emission tomography. Neurosci. Lett. 245, 1):1–4 (Epub 1998/05/22. PubMed PMID: 9596341).
Myrseth, E., Moller, P., Pedersen, P.H., Vassbotn, F.S., Wentzel-Larsen, T., Lund-Johansen, M., 2005. Vestibular schwannomas: clinical results and quality of life after microsurgery or gamma knife radiosurgery. Neurosurgery. 56 (5), 927–935 discussion -35. (Epub 2005/04/28. PubMed PMID: 15854240).
Myrseth, E., Moller, P., Wentzel-Larsen, T., Goplen, F., Lund-Johansen, M., 2006a. Untreated vestibular schwannomas: vertigo is a powerful predictor for health-related quality of life. Neurosurgery. 59 (1), 67–76. discussion 67-76. Epub 2006/07/11. https://doi.org/10.1227/01.NEU.0000219838.80931.6B (PubMed PMID: 16823302).
Myrseth, E., Moller, P., Wentzel-Larsen, T., Goplen, F., Lund-Johansen, M., 2006b. Untreated vestibular schwannoma: vertigo is a powerful predictor for health-related quality of life. Neurosurgery. 59 (1), 67–76. Epub 2006/07/01. https://doi.org/10.1227/01.neu.0000243285.06415.4c (PubMed PMID: 28180608).
Norrelgen, F., Lilja, A., Ingvar, M., Amark, P., Fransson, P., 2015. Presurgical language lateralization assessment by fMRI and dichotic listening of pediatric patients with intractable epilepsy. Neuroimage Clin 7, 230–239. Epub 2015/01/23. https://doi.org/10.1016/j.nicl.2014.12.011 (PubMed PMID: 25610785; PubMed Central PMCID: PMCPMC4300009).
Osnes, B., Hugdahl, K., Specht, K., 2011. Effective connectivity analysis demonstrates involvement of premotor cortex during speech perception. Neuroimage. 54 (3), 2437–2445. Epub 2010/10/12. https://doi.org/10.1016/j.neuroimage.2010.09.078 (PubMed PMID: 20932914).
Peelle, J.E., 2018. Listening effort: how the cognitive consequences of acoustic challenge are reflected in brain and behavior. Ear Hear. 39 (2), 204–214. Epub 2017/09/25. https://doi.org/10.1097/AUD.0000000000000494 (PubMed PMID: 28938250; PubMed Central PMCID: PMCPMC5821557).
Propst, E.J., Greinwald, J.H., Schmithorst, V., 2010. Neuroanatomic differences in children with unilateral sensorineural hearing loss detected using functional magnetic resonance imaging. Arch. Otolaryngol. Head Neck Surg. 136 (1), 22–26. Epub 2010/01/20. https://doi.org/10.1001/archoto.2009.208 (PubMed PMID: 20083773).
Pross, S.E., Chang, J.L., Mizuiri, D., Findlay, A.M., Nagarajan, S.S., Cheung, S.W., 2015. Temporal cortical plasticity in single-sided deafness: a functional imaging study. Otol Neurotol. 36 (8), 1443–1449. Epub 2015/07/22. https://doi.org/10.1097/MAO.0000000000000821 (PubMed PMID: 26196207).
Salvi, R.J., Lockwood, A.H., Frisina, R.D., Coad, M.L., Wack, D.S., Frisina, D.R., 2002. PET imaging of the normal human auditory system: responses to speech in quiet and in background noise. Hear. Res. 170 (1-2), 96–106 Epub 2002/09/05. (PubMed PMID: 12208544).
Scheffler, K., Bilecen, D., Schmid, N., Tschopp, K., Seelig, J., 1998. Auditory cortical responses in hearing subjects and unilateral deaf patients as detected by functional magnetic resonance imaging. Cereb. Cortex 8 (2), 156–163 (Epub 1998/05/30. PubMed PMID: 9542894).
Schmithorst, V.J., Holland, S.K., Ret, J., Duggins, A., Arjmand, E., Greinwald, J., 2005. Cortical reorganization in children with unilateral sensorineural hearing loss. Neuroreport. 16 (5), 463–467 (Epub 2005/03/17. PubMed PMID: 15770152; PubMed Central PMCID: PMCPMC1357558).
Sequeira Sdos, S., Specht, K., Hamalainen, H., Hugdahl, K., 2008. The effects of different intensity levels of background noise on dichotic listening to consonant-vowel syllables. Scand. J. Psychol. 49 (4), 305–310. Epub 2008/05/21. https://doi.org/10.1111/j.1467-9450.2008.00664.x (PubMed PMID: 18489535).
Shargorodsky, J., Curhan, G.C., Farwell, W.R., 2010. Prevalence and characteristics of tinnitus among US adults. Am. J. Med. 123 (8), 711–718. Epub 2010/07/31. https://doi.org/10.1016/j.amjmed.2010.02.015 (PubMed PMID: 20670725).
Specht, K., 2014. Neuronal basis of speech comprehension. Hear. Res. 307, 121–135. Epub 2013/10/12. https://doi.org/10.1016/j.heares.2013.09.011 (PubMed PMID: 24113115).
Specht, K., Reul, J., 2003. Functional segregation of the temporal lobes into highly differentiated subsystems for auditory perception: an auditory rapid event-related fMRI-task. Neuroimage. 20 (4), 1944–1954 Epub 2003/12/20. (PubMed PMID: 14683700).
Specht, K., Wigglesworth, P., 2018. The functional and structural asymmetries of the superior temporal sulcus. Scand. J. Psychol. 59 (1), 74–82. Epub 2018/01/23. https://doi.org/10.1111/sjop.12410 (PubMed PMID: 29356006).
Specht, K., Rimol, L.M., Reul, J., Hugdahl, K., 2005. "Soundmorphing": a new approach to studying speech perception in humans. Neurosci. Lett. 384 (1-2), 60–65. Epub 2005/05/24. https://doi.org/10.1016/j.neulet.2005.04.057 (PubMed PMID: 15908119).
Specht, K., Osnes, B., Hugdahl, K., 2009. Detection of differential speech-specific processes in the temporal lobe using fMRI and a dynamic "sound morphing" technique. Hum. Brain Mapp. 30 (10), 3436–3444. Epub 2009/04/07. https://doi.org/10.1002/hbm.20768 (PubMed PMID: 19347876).
Tharpe, A.M., Sladen, D.P., 2008. Causation of permanent unilateral and mild bilateral hearing loss in children. Trends Amplif 12 (1), 17–25. Epub 2008/02/14. https://doi.org/10.1177/1084713807313085 (PubMed PMID: 18270175; PubMed Central PMCID: PMCPMC4111449).
Vila, P.M., Lieu, J.E., 2015. Asymmetric and unilateral hearing loss in children. Cell Tissue Res. 361 (1), 271–278. Epub 2015/05/26. https://doi.org/10.1007/s00441-015-2208-6 (PubMed PMID: 26004144; PubMed Central PMCID: PMCPMC4490007).
Wilke, M., Lidzba, K., 2007. LI-tool: a new toolbox to assess lateralization in functional MR-data. J. Neurosci. Methods 163 (1), 128–136. Epub 2007/03/28. https://doi.org/10.1016/j.jneumeth.2007.01.026 (PubMed PMID: 17386945).
Wilke, M., Schmithorst, V.J., 2006. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. Neuroimage. 33 (2), 522–530. Epub 2006/08/30. https://doi.org/10.1016/j.neuroimage.2006.07.010 (PubMed PMID: 16938470).
Wilke, M., Lidzba, K., Staudt, M., Buchenau, K., Grodd, W., Krageloh-Mann, I., 2006. An fMRI task battery for assessing hemispheric language dominance in children. Neuroimage. 32 (1), 400–410. Epub 2006/05/03. https://doi.org/10.1016/j.neuroimage.2006.03.012 (PubMed PMID: 16651012).
Zatorre, R.J., Belin, P., 2001. Spectral and temporal processing in human auditory cortex. Cereb. Cortex 11 (10), 946–953 (Epub 2001/09/11. PubMed PMID: 11549617).
Zhang, Y., Mao, Z., Feng, S., Wang, W., Zhang, J., Yu, X., 2018. Convergent and divergent functional connectivity patterns in patients with long-term left-sided and right-sided deafness. Neurosci. Lett. 665, 74–79. Epub 2017/11/28. https://doi.org/10.1016/j.neulet.2017.11.050 (PubMed PMID: 29175032).