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Research Paper

Hyperacusis in tinnitus patients relates to enlarged subcortical and cortical responses to sound except at the tinnitus frequency

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ABSTRACT

Hyperacusis, a hypersensitivity to sounds of mild to moderate intensity, has been related to increased neural gain along the auditory pathway. To date, there is still uncertainty on the neural correlates of hyperacusis. Since hyperacusis often co-occurs with hearing loss and tinnitus, the effects of the three conditions on cortical and subcortical structures are often hard to separate. In this fMRI study, two groups of hearing loss and tinnitus participants, with and without hyperacusis, were compared to specifically investigate the effect of the latter in a group that often reports hyperacusis. In 35 participants with hearing loss and tinnitus, with and without hyperacusis as indicated by a cut-off score of 22 on the Hyperacusis Questionnaire (HQ), subcortical and cortical responses to sound stimulation were investigated. In addition, the frequency tuning of cortical voxels was investigated in the primary auditory cortex. In cortical and subcortical auditory structures, sound-evoked activity was higher in the group with hyperacusis. This effect was not restricted to frequencies affected by hearing loss but extended to intact frequencies. The higher subcortical and cortical activity in response to sound thus appears to be a marker of hyperacusis. In contrast, the response to the tinnitus frequency was reduced in the group with hyperacusis. This increase in subcortical and cortical activity in hyperacusis can be related to an increase in neural gain along the auditory pathway, and the reduced response to the tinnitus frequency to differences in attentional resources allocated to the tinnitus sound.

1. Introduction

Hyperacusis is characterized by the experience of uncomfortable loudness for sounds that are not uncomfortably loud to most people (Anari et al., 1999; Baguley, 2003). In other words, this heightened sensitivity to sound intensity occurs in response to soft and moderate sounds. Hyperacusis often co-occurs with hearing loss, 59.1% of people with hyperacusis also have hearing loss according to a physician established incidence report (Paulin et al., 2016). In hearing loss, loudness perception is altered due to a reduction in the dynamic input range that results in a diminished loudness output range. Consequently, a steeper increase in loudness ensues, or loudness recruitment, for frequencies affected by the hearing loss. In hyperacusis, the loudness recruitment is often steeper than in hearing loss alone and can be present without a reduction in the dynamic input range. In addition to comorbidity with hearing loss, hyperacusis often co-occurs with tinnitus, with an estimated prevalence of 55–86 % of hyperacusis in tinnitus patients (Anari et al., 1999; Dauman and Bouscau-Faure, 2005; Schecklmann et al., 2014). Tinnitus is the perception of sound in the absence of an external source. It is a common symptom that occurs in 12–30 % of the general population, although prevalence estimates of tinnitus vary (McCormack et al., 2016). The prevalence rises to higher estimates with increasing age, and tinnitus is present in the majority of people with hearing loss (Tan et al., 2013). Both hyperacusis and tinnitus are debilitating symptoms, and even though several treatment options are available, there is presently no cure for either condition.

Currently, there is no comprehensive knowledge of the mechanisms behind tinnitus and hyperacusis. Hyperacusis and hearing loss have been explained by non-linear neural gain models Diehl and Schaette (2015) and investigated with animal experimental work (Auerbach et al., 2019). According to the neural gain model, neural gain in the central auditory pathway is triggered

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by a decrease in peripheral input Schaette and Kempter (2006). This reduction in input corresponds to hearing loss. Within this model, hyperacusis is hypothesized to result from abnormal gain along the auditory pathway in response to sound-evoked activation (Gu et al., 2010; Diehl and Schaette, 2015). In contrast to sound-evoked activation, tinnitus is explained by the amplification of spontaneous neural activity in the central auditory system in a manner similar to sound-evoked activity, causing the spontaneous activity to cross the threshold of perception (Auerbach et al., 2014; Diehl and Schaette, 2015). However, whereas this framework of neural gain can incorporate that tinnitus and hyperacusis do not always co-occur Penner (1986), it does not incorporate that hearing loss is not always present in hyperacusis or tinnitus (Tan et al., 2013). Other models of tinnitus proposed that tinnitus results from increased central noise, a different mechanism from the increased non-linear gain implicated in hyperacusis and hearing loss (Knipper et al., 2013; Zeng, 2013). In this view, tinnitus is associated with reduced gain in the auditory pathway (Hofmeier et al., 2018), and reduced connectivity along the auditory pathway (Boyen et al., 2014; Lanting et al., 2016). Therefore, two different pathways are proposed for the origins of tinnitus and hyperacusis, whereas central gain is specifically related to hyperacusis, tinnitus may be related to increased central noise in the auditory system.

To date, there is still uncertainty on the neural correlates of hearing loss, tinnitus, and hyperacusis. Since these conditions often co-occur, this hampers the separation of their effects on the central auditory system. Previous neuroimaging studies indicate that both subcortical and cortical sound-evoked activity is increased in the presence of hyperacusis (Gu et al., 2010; Knipper et al., 2013; Rüttiger et al., 2013; Chen et al., 2015). In other studies, both tinnitus and hyperacusis were co-occurring and consequently, the effects of both conditions proved difficult to disentangle since their co-occurrence was not controlled for(Lanting et al., 2008; Melcher et al., 2009). Previous studies that specifically focused on hyperacusis were performed with individuals with no or minimal hearing loss. In general, tinnitus patients with hearing loss are underrepresented in these fMRI studies on hyperacusis even though tinnitus, hearing loss, and hyperacusis often co-occur.

The current study aims to specifically evaluate subcortical and cortical responses in tinnitus patients with and without hyperacusis. A distinctive characteristic of this study, and our previous study (Koops et al., 2020), is the focus on individuals with moderate sensorineural hearing loss, a group that is often encountered in tinnitus clinics. Subcortical responses to sound stimulation were investigated for tinnitus patients with and without hypersensitivity to sound, as indicated by a score of $\geq$ 22 on the Hyperacusis Questionnaire Aazh and Moore (2017). In addition, cortical sound-evoked responses, the cortical response to the presentation of the tinnitus frequency, and the tuning of cortical voxels were investigated in the auditory cortex of tinnitus patients with and without hypersensitivity to sound.

2. Materials and methods

The medical ethical committee of the University Medical Center of Groningen, the Netherlands, approved this study. The study was performed in accordance with the principles of the declaration of Helsinki (2013), and participants received reimbursement for their time and signed a written informed consent.

2.1. Participants

In the context of a larger MRI study (Koops et al., 2020), 35 participants with hearing loss and tinnitus were included. Hearing thresholds were obtained in a sound-attenuating booth for octave frequencies 0.125 to 8 kHz, and additional for 3 and 6 kHz. None of the participants used hearing aids to compensate for their hearing loss or improve their tinnitus. All participants were requested to fill in the Hospital Anxiety and Depression Scale Zigmond and Snaith (1983), the Hyperacusis Questionnaire (Khalfa et al., 2002), the Tinnitus Handicap Inventory (McCombe et al., 2001), and the Tinnitus Reactions Questionnaire (Wilson et al., 1991). Hyperacusis was defined as an HQ score of 22 or higher, in line with the recommendation of Aazh and Moore (2017).

Care was taken to prevent discomfort for participants during participation in this study. The recruitment advertisement specifically noted that MRI research is rather noisy. During contact with the researcher, either via e-mail or a phone call, it was stressed that although the sound levels within the MRI are not harmful with the earphones on, the scanner noise is still loud. Despite our precautions, two participants expressed discomfort during the scanning procedures described below.

For the variable sex, group differences were tested with a Chi-square test of independence. For the variables age and tinnitus duration, an independent pairwise t-test was used. Group differences in hearing thresholds, stimulation intensity, questionnaire scores, and tinnitus loudness and pitch were tested using an independent-sample Mann–Whitney U test.

2.2. Experimental design

2.2.1. Data acquisition

A 3.0 T Philips Intera MRI scanner (Best, the Netherlands), equipped with a SENSE 32-channel head coil, situated at the NeuroImaging Center in Groningen was used to acquire the MRI scans. A sparse imaging paradigm was used to obtain the functional volumes and minimize interference of scanner noise with the auditory task (Hall et al., 1999). A whole brain structural T1 weighted scan (1 mm x 1 mm x 1 mm) was obtained in the same session to facilitate co-registration and normalization of the functional MRI scans. The functional images were acquired in 47 slices, single-shot EPI with no gap, in descending order with a scan matrix of 72 $\times$ 67, FOV 210 $\times$ 210 $\times$ 141, and a TR of 10 s, TE 22 ms, Flip Angle 90°. A total of three runs of 65 EPI volumes, lasting 10 min per run, were acquired for each participant. A single brain volume acquisition consisted of 2 s of scanning and was preceded by a stimulus of 7.5 s duration. This sparse sampling protocol was employed to ensure that the sound presentation coincided with the relative quiet of the interscan intervals.

2.2.2. Sound stimuli

Each participant performed a binaural loudness matching task prior to the MRI scanning, where they matched the perceived loudness of tones at 0.25,0.5,2, 4, and 8 kHz to that of a 1 kHz tone at 40 dB SPL. To obtain an equal-loudness contour for each participant, a two alternative-forced-choice interleaved staircase procedure was used with 15 trials per frequency, 7 reversals, and a step size of [10,5,5,3,3,1,1] dB. All participants performed the loudness matching task twice, to ensure proper understanding of the task. The thresholds from the second trial of the loudness matching task were used to set the intensities for the stimuli presented during the MRI scanning. Both the headphones used in the MRI and the headphones used in the sound-attenuating booth were calibrated with a B&K 4134 microphone inserted in the ear of a KEMAR dummy. Loudness matching was performed to improve comparability between participants, since both participants with and without hearing loss were included in the larger fMRI-study. Thus, the use of loudness matching established audibility of the stimuli for all participants, with and without hearing loss, and equal loudness over frequencies within a participant. The use of loudness-based stimuli builds on the finding that sound-evoked cortical

activation correlates well with the perceived loudness of a tone in both normal-hearing participants and hearing-impaired participants (Langers et al., 2007). Additionally, loudness correlates better with the Blood Oxygenation Response Levels, used in fMRI, than sound intensity (Hall et al., 2001; Langers et al., 2007).

2.2.3. Procedure MRI

All sound conditions, i.e. loudness-matched tones at frequencies ranging from 250–8000 Hz and a silence condition, were presented binaurally in a quasi-random order. The stimuli consisted of tones of 245 ms in duration at a 4 Hz repetition rate, with the total duration of sound stimulation lasting for 7.5 s for each volume acquisition. An MR Confon Sound System (Baumgart et al., 1998) was used to deliver the sound stimuli in the MRI during the sparse-sampling protocol. Simultaneously with the presentation of the auditory stimuli, participants performed a visual valence task (Langers et al., 2012). In order to control for attention, participants were instructed to focus on and respond to the visual valence task.

2.3. Statistical analyses

2.3.1. Data preprocessing

Data analysis was performed with SPM12 (Statistical Parametric Mapping) and MATLAB (version 2020a). The functional MRI images were first realigned, then co-registered to the anatomical image, and normalized to fit a standard MNI brain which resulted in the reslicing of the images to an isotropic voxel-size of 2 mm. Smoothing was performed with a full-width half-maximum Gaussian kernel of 5 mm. A logarithmic transformation was used to convert the fMRI output into percentage signal change Langers and van Dijk (2012).

2.3.2. Subcortical regions-of-interest

The subcortical auditory regions incorporated in the subcortical mask were drawn in Mrtrix (Tournier et al., 2019) on the anatomical SPM12 MNI-template. Regions included are the Cochlear Nucleus (CN), Superior Olivary Complex (SOC), Inferior Colliculus (IC), and Medial Geniculate Area (MGB) of the thalamus. The MGB and IC are recognizable on an anatomical template, whereas the CN and SOC are not. For the CN and SOC, we based the location of our ROIs on a recent functional imaging study identifying activation in these areas (Sitek et al., 2019). Masks were drawn larger than the actual structure to ensure that all of the intended areas was included. FSL was used to combine these regions into a single template. Group differences were tested with a two-sample *t*-test.

In addition to the ROI analysis, average percentage signal change in response to sound was calculated for each subcortical region for all voxels that showed a significant response to sound at FDR < 0.05. Differences in sound-evoked responses were tested with a repeated measures ANOVA to investigate differences within subjects over auditory areas and to compare the subcortical and cortical activation of participants with high (≥ 22) and low scores (<22) on the Hyperacusis Questionnaire. For each voxel that showed a significant difference in activation, it was determined with the MNI template and FSLeyes (0.26.1; McCarthy, 2020) if this voxel was indeed part of the auditory subcortical structures.

Furthermore, two-sample *t*-tests were performed to investigate the presence of frequency-specific differences in subcortical activation between the groups with high and low HQ scores. Finally, the subcortical response to the tinnitus frequency, or the frequency closest to the tinnitus frequency, was compared between the groups with high and low scores on the HQ. This was done by means of a two-sample permutation *t*-test ($n = 5000$), permuting the participants over the groups.

2.3.3. Cortical regions-of-interest

The cortical region-of-interest analyses were masked by the anatomical Brodmann areas 41, 42, and 22 that correspond to the auditory cortex. These masks were defined with WFU Pickatlas (Maldjian et al., 2003). Brodmann area 41 corresponds to the primary auditory cortex, Brodmann area 42 to the secondary auditory cortex, and Brodmann area 22 is the association auditory cortex. Average percentage signal change in response to sound was calculated for the primary, secondary, and association auditory cortex. Furthermore, for these areas, the average response per frequency was calculated. Two-sample t-tests were performed per frequency response to test for frequency-specific differences in the auditory cortex (BA41, BA42, BA22) between tinnitus participants with high and low scores on the HQ. Finally, the cortical response to the tinnitus frequency, or the frequency closest to the tinnitus frequency, was compared between the groups with high and low scores on the HQ. Statistical testing was performed with a permutation ($n = 5000$) two-sample *t*-test, permuting the participants over the groups.

2.3.4. Tuning of cortical voxels

For all participants, a voxel tuning measure was derived for the cortical region of Brodmann area (BA) 41, based on a 'best frequency' tonotopic map (Berlot et al., 2020). For every voxel, the frequency condition that elicited the highest response was obtained and the voxels were classified according to this peak-frequency responsiveness. This was performed for the voxels that were significantly activated within the anatomical mask of BA 41 in response to sound at an FWE p-value of < 0.05. The tuning of each voxel was then determined by the responses of the voxels in BA 41 to the 6 presented frequencies (i.e. both for the amplitude in response to the preferred frequency and for the amplitude in response to non-preferred frequencies), in line with the method proposed in the paper of Berlot et al., 2020. The largest response, or best frequency, was normalized to 1. A permutation two-sample *T*-test ($n = 5000$) on the average of the non-preferred frequencies, where the participants were permuted over the groups, was used to compare the voxel tuning of the tinnitus group with high HQ and low HQ scores. This analysis was performed for the non-preferred frequencies, i.e. the 2nd and 3rd frequency away from the preferred frequency. The permutation testing was done by extracting the responses to the best and non-preferred frequencies on a per frequency level, these responses were normalized and pooled to obtain a matrix with responses to the non-preferred frequencies for each BF. If there was a second frequency away from the BF on either side of the BF, the average of these was taken.

3. Results

3.1. Behavioural results

In total, 11 of the participants had a hyperacusis (HQ) score $\geq$ 22. For the remaining 24 participants, the hyperacusis score was below 22. Hearing thresholds were not significantly different between the groups with high and low HQ scores, as shown by an independent-samples Mann-Whitney U-Test (see Fig. 1 A). In line with this, there were no significant differences in the intensity of the stimuli presented during scanning (see Fig. 1 B). Additionally, the groups were not significantly different in terms of sex distribution ($p = 0.392$), age ($t = 0.159$, $p = 0.875$), or tinnitus pitch ($p = 0.91$) and loudness ($p = 0.88$). The group with higher HQ scores had a significantly longer duration of tinnitus ($t = 2.3$, $p = 0.031$), and higher THI total scores ($p = 0.005$). There were no significant differences in terms of scores on the HADS Anxiety ($p = 0.195$) or Depression scale ($p = 0.08$), although the effect on the latter approached significance. See Table 1.

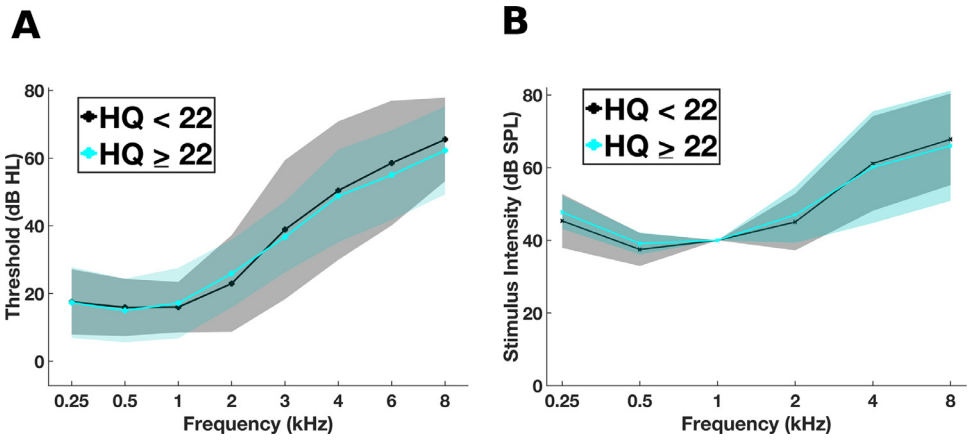

Fig. 1. (A) Mean audiometric thresholds of participants. Shading indicates group standard deviations. In black, the mean thresholds of participants with HQ scores < 22, and in blue the mean thresholds of participants with HQ scores ≥22. There are no significant differences between the groups on any of the frequencies (250 Hz $p = 0.64$; 500 Hz $p = 0.77$; 1 kHz $p = 0.69$; 2 kHz $p = 0.47$; 3 kHz $p = 0.79$; 4 kHz $p = 0.71$; 6 kHz $p = 0.52$; 8 kHz $p = 0.39$). (B) Intensity of loudness matched stimuli presented during MRI scanning. All stimuli were matched in loudness to a 1 kHz tone at 40 dB SPL, resulting in a 40-phon loudness contour. Depicted are the averaged intensities of the presented stimuli and the corresponding group standard deviations.

Table 1
Demographical information and questionnaire scores of the two groups.

Groups	HQ < 22	HQ ≥ 22
Demographics	N = 24	N = 11
Sex	19 M, 5 F	10 M, 1 F
Mean age (years)	59 ± 11 (26-72)	59 ± 9 (41-73)
Questionnaires		
HADS Anxiety	4 ± 3 (0-11)	6 ± 4 (0-12)
HADS Depression	4 ± 3 (0-8)	7 ± 4 (0-16)
HQ	12 ± 6 (0-21)	28 ± 5 (22-37)*
THI	27 ± 19 (4- 76)	48 ± 19 (20- 82)*
Tinnitus		
Mean duration (years)	10 ± 6 (2-20)	17 ± 9 (1-33)*
Tinnitus Pitch	1 - 4 kHz (n = 8)	1 - 4 kHz (n =5)
	5 - 7 kHz (n = 3)	5 - 7 kHz (n = 2)
	≥8 kHz (n = 9)	≥8 kHz (n = 4)
	Broad Band (n = 4)	
Tinnitus loudness	60 dB HL ± 17 (30-100)	61 dB HL ± 16 (40-85)

* indicates that groups differed significantly from one another at p < 0.001. Chi-square, ANOVA, Kruskal-Wallis and Mann-Whitney respectively

3.2. Subcortical responses increased in hyperacusis

In the subcortical auditory pathway, the comparison of sound-evoked activation in participants with high versus low HQ-scores showed that higher hyperacusis scores were related to higher sound-evoked responses in the area of the bilateral superior olivary complex, the right inferior colliculus, and right medial geniculate body. See Table 2 and Fig. 2. This region of interest analysis identified specific voxels that showed a difference in responsiveness. Whereas we could obtain significant responses in the subcortical areas when we investigated the responses to all sound conditions together, we could not robustly identify significant activation in all subcortical ROIs if we included only one frequency at a time. Therefore, we could not specify if there were frequency-specific differences in subcortical sound-evoked activation between the groups.

In light of the central gain theory, we investigated if a clear increase in response to sound could be observed along the auditory neuraxis. In Fig. 3 A, the average response to all sound conditions is depicted for each auditory area. To test for both within-participant and group differences in activation over subcortical and cortical areas, a repeated-measures ANOVA was applied. The assumption of sphericity was violated according to a Mauchly's Test of Sphericity ($\chi^2(20) = 97.4$, $p < 0.005$, and therefore a Greenhouse-Geisser correction was applied. There was no significant effect of area on activity levels within participants, $F(3.083,102) = 2.481$, $p = 0.064$). There was a significant effect of group on percentage signal change in the auditory areas after Bonferroni correction for multiple comparisons ($F = 10.25$, $p = 0.003$). The average sound-evoked response for each group and auditory area is depicted in Fig. 3 A. The previous ROI analysis showed that specific voxels within the auditory subcortical structures showed a significant increase in activity in response to sound for the group with high HQ scores. Similarly, the group with high HQ scores had higher average activity over all auditory subcortical and cortical regions.

3.3. Frequency specific cortical responses

On a cortical level, high HQ scores resulted in significantly higher activation in BA 41, BA 42, and BA 22 in response to sound if the combined responses of all sound conditions were considered (FWE (RFT) < 0.05; Fig. 4 A). In a frequency-wise analysis, it appeared that the amplitudes of the frequency responses in BA 41 are almost twice that of those in BA 22 (see Fig. 4 B and D). These differences in amplitude between BA 41 and BA 22 were significant for the group with high HQ-scores ($t = 3.5$, $p_{perm} = 0.0054$) but not for the group with low HQ-scores ($t = 0.38$, $p_{perm} = 0.72$). A frequency-specific difference in amplitude was identified at 250 Hz, with the high HQ-score group having significantly increased responses in BA 41 ($p = 0.018$), BA 42 ($p = 0.0289$), and BA 22 ($p = 0.024$) (Fig. 4 B, C, and D). In addition, in BA 41 higher responses to 4 kHz were observed in the group with high HQ-scores ($p = 0.024$). These effects are not significant after correcting for multiple comparisons in the strictest sense ($p < 0.0083$). Even though there are significant group differences in overall responsiveness to sound for all three auditory cortex areas, there are no frequency-specific differences that remain after stringent correction for multiple comparisons.

Furthermore, we tested for group differences in the average cortical sound-evoked response to the tinnitus frequency (or the closest match). In response to the tinnitus frequency, a significantly higher response was observed for the tinnitus group with low HQ-scores, for both the left primary auditory cortex ($t = 22.4$, $p_{perm} = 0.0352$) and the right primary auditory cortex ($t = 16.95$, $p_{perm} = 0.0412$), see Fig. 3 B. Similarly, a higher response to the tinnitus frequency was observed for the group with low HQ scores in the secondary, and association auditory cortices, although this

Table 2
Region-of-interest analysis comparing high vs low HQ scores in hearing loss and tinnitus participants. Significance, cluster size, T values, and MNI coordinates of the region of interest analyses are displayed. A mask was drawn on the MNI template and included the bilateral cochlear nucleus, superior olivary complex, inferior colliculus, and medial geniculate. The significant differences are reported in the table.

Cluster level			Peak level				Area	
FWE-corrected	*k*	*p*	*T*	*MNI Coordinates*			*Lat*	*Region*
				x	*y*	*z*		
	3	0.011	4.9	6	-32	-8	R	Inferior Colliculus
	4	0.008	4.4	8	-34	-36	R	Superior Olivary Complex
	2	0.016	4.3	-4	-34	-34	L	Superior Olivary Complex
	3	0.044	3.4	18	-22	10	R	Medial Geniculate Nucleus

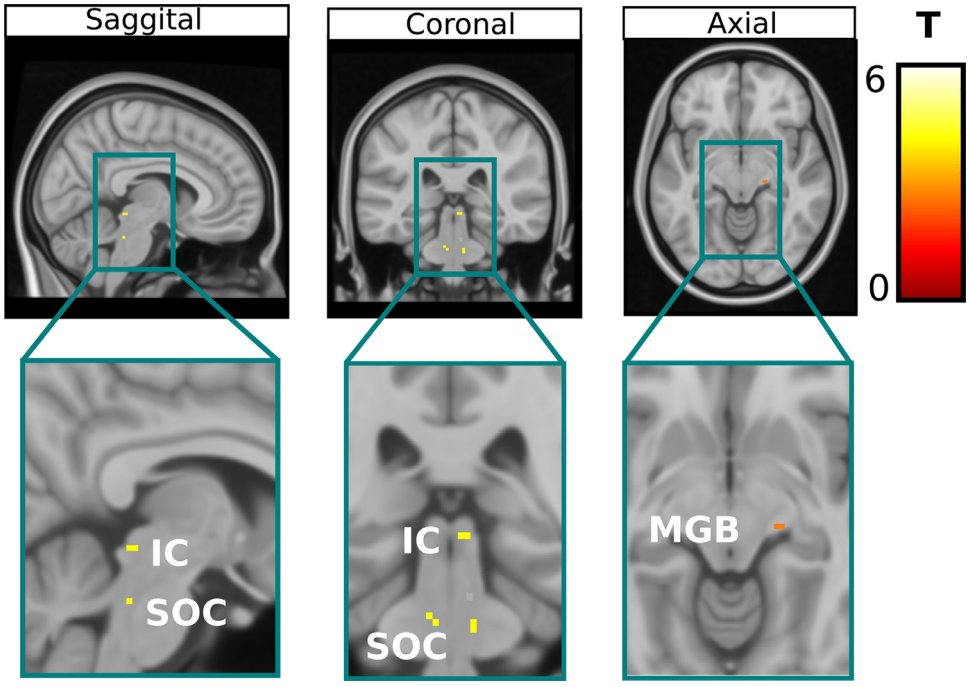

Fig. 2. Increased sound-evoked activation in the group with higher HQ scores vs the group with lower HQ scores. In the panels of the sagittal, axial, and coronal view, an enlarged area of the increased activation is shown. All voxels indicated here showed a significant difference in activation at an FWE-level of 0.05. See also Table 2.

effect did not reach significance (L BA42: $T = 2.9$, $p_{perm} = 0.6$; RBA42: $T = 7.8$, $p_{perm} = 0.1$; L BA22: $T = 9.3$, $p_{perm} = 0.3$; R BA22: $T = 10.9$, $p_{perm} = 0.14$); see Fig. 3 B. To test if this significant group difference in the response of the primary auditory cortex to the tinnitus frequency is related to the reported difference in the duration of tinnitus, duration was included as a continuous covariate of no interest before rerunning the tinnitus response analysis. This did not alter the results. Therefore, the difference in response to the tinnitus frequency is not explained by the difference in tinnitus duration and is likely related to the presence or absence of hyperacusis.

We performed an additional sensitivity analysis using an HQ cut-off score of 16, as proposed by Fioretti et al., 2015. The results of this analysis show that with an HQ cut-off score of 16 there are fewer voxels in the auditory cortex (BA41, BA42, and BA22) that show a statistically significant difference in the group comparison, see suppl. Fig. 1 A. The average responses in the cortical areas are still higher in the group with high HQ-scores ($\geq$ 16) than those with lower HQ-scores. However, this difference between the groups is smaller than in the group comparison with an HQ cut-off score of 22, see suppl. Fig. 1 (B, C, D). This sensitivity analysis shows that whereas an HQ cut-off score of 22 can be related to a significant increase in cortical responsiveness to sound, an HQ cut-off score of 16 does not reflect a significant increase in activity. It thus appears that, in light of the hypothesis that an increase in central gain is related to hyperacusis, an HQ cut-off score of 22 does reflect this whereas an HQ cut-off score of 16 does not.

3.4. Cortical tuning in response to sound in hyperacusis

The tuning curves of voxel responses in the primary auditory cortex, where the response to the frequency that elicited the largest response was normalized to 1, are displayed in Fig. 5. This frequency is referred to as the best frequency (BF). Below and above the BF, the responses were by definition smaller than 1 (see Fig. 5 A and B). A two-sample permutation t-test on the average of the non-preferred frequencies (2^{nd} and 3^{rd} frequency away from the preferred frequency of a voxel) showed that this difference was not significant (L BA41: $t = 1.94$, $p_{perm} = 0.055$; R BA41 $t = 1.54$, $p_{perm} = 0.13$). Thus, these results do not provide evidence for a difference in the cortical tuning of the auditory cortex in tinnitus with and without hyperacusis.

4. Discussion

We investigated the effect of hyperacusis on cortical and subcortical sound-evoked auditory activity in participants with tinnitus and hearing loss. The specific impact of hyperacusis was

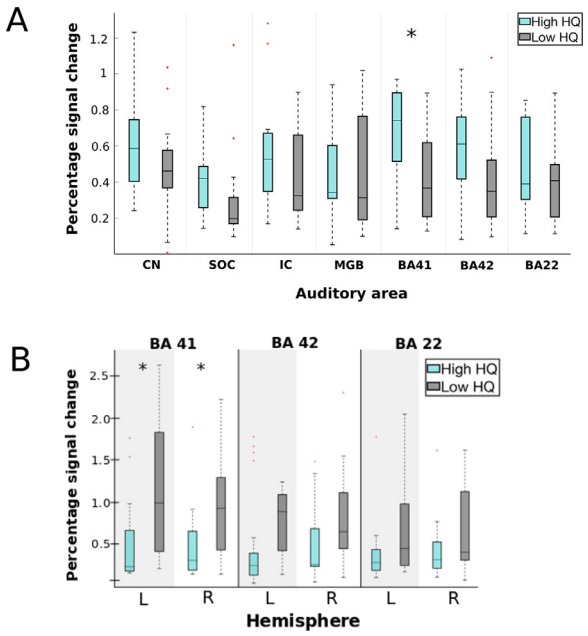

Fig. 3. (A) Average sound-evoked responses in brain areas along the central auditory pathway. The averaged responses to sound of the various auditory areas included in our analyses are presented for the group with low and high HQ scores. (B) Response of the auditory cortex to a sound stimulus at the tinnitus frequency. For both groups, the average sound-evoked responses to the individual tinnitus frequency, or the frequency closest to that, are depicted for the left and right hemispheres. The group with low HQ scores has a significantly higher response in BA 41 to the tinnitus sound, indicated by the asterisks.

investigated by comparing two participant groups with similar tinnitus and hearing loss were compared, one with and one without hyperacusis. On a subcortical level, increased responses were observed in the right medial geniculate, inferior colliculus, and the bilateral superior olivary complex of participants with hyperacusis. On a cortical level, our results show a relation between hyperacusis and increased overall sound-evoked activation in the primary, secondary, and association auditory cortex. Altogether, higher subcortical and cortical activity in response to sound thus appears to be a marker of hyperacusis.

4.1. Subcortical and cortical responses to sound in the presence of hyperacusis

These findings replicate the findings of previous publications on human and animal studies (Gu et al., 2010; Knipper et al., 2013; Rüttiger et al., 2013; Zeng, 2013; Chen et al., 2015; Auerbach et al., 2019). In our study, tinnitus participants had additional and pronounced hearing loss which contrasts with the previous human studies that included participants with no or minimal hearing loss. To account for differences in hearing loss within our study, we carefully loudness matched all stimuli on an individual basis. This loudness matching implies that each participant perceived the different frequencies as equally loud, regardless of their hearing loss. Nonetheless, the observed increased responses to sound in participants with higher HQ-scores suggest that in the presence of hyperacusis the overall perceived loudness of the stimuli may have been higher. Generally, similar to the study of Gu et al (2010), our participants had mild hyperacusis, as it was not their primary complaint and was only rarely mentioned during the interview. In the current study, increased responses to sound were present in hyperacusis and overt hearing loss, which is in line with former studies that reported increased activity in hyperacusis with minimal hearing loss. Thus, it appears that even in milder forms, and in the presence of hearing loss and tinnitus, the subcortical and cortical responses to sound are increased in the presence of hyperacusis.

4.2. Relation between loudness and increased activation in auditory brain areas

To expand on the possible increase in perceived loudness in the presence of hyperacusis, it must be noted that both increases in intensity and broadening of bandwidth increase the perceived loudness of sound stimuli, as described by Gu et al., 2010 (Zwicker et al., 1957; Hawley et al., 2005). Normally, a stimulus that excites several frequency channels of the auditory system

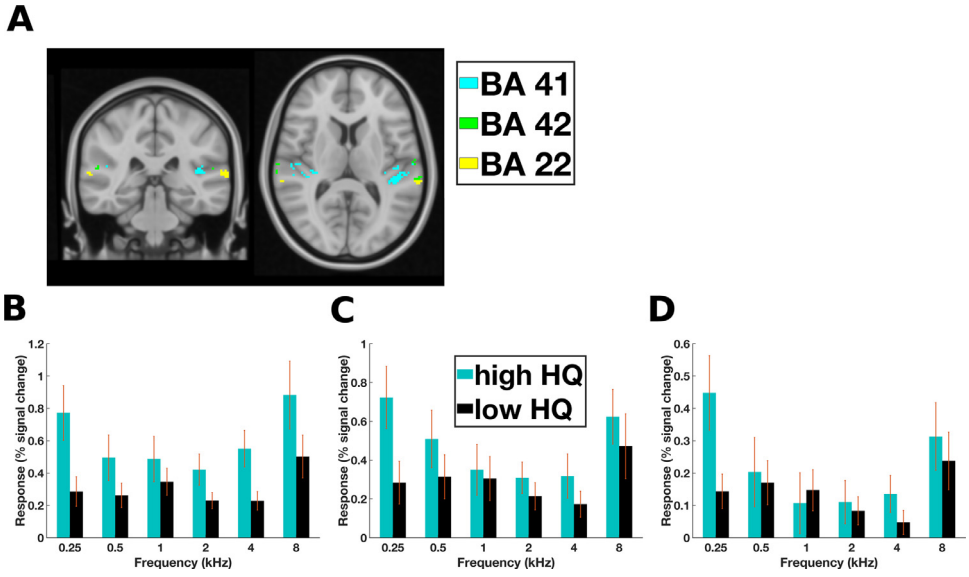

Fig. 4. Cortical sound-evoked activity was higher in tinnitus participants with high HQ scores than with low HQ scores. (A) In colour, the voxels with overall higher activity in response to sound in the group with high HQ scores (FWE < 0.05). Here, the combined responses to all sound conditions was considered. In blue, for those with higher HQ scores the voxels with higher activity in BA 41, in green for BA42, and in yellow for BA22. (B) Responses in the bilateral primary auditory cortex (BA41). (C) Responses in the secondary auditory cortex (BA 42). (D) Responses in the association auditory cortex (BA 22). Mean responses and their standard errors are shown for the group with high HQ scores and the group with low HQ scores. The amplitude of responses is plotted per frequency.

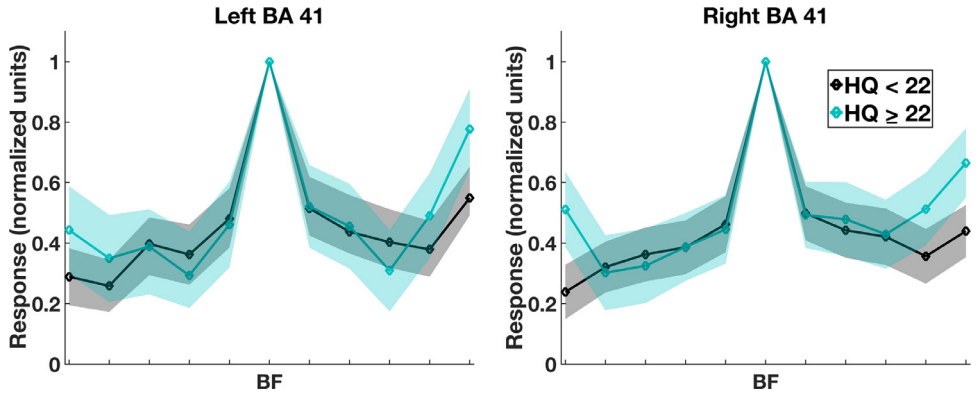

Fig. 5. Average tuning curves of voxels in the primary auditory cortex. For each voxel, the response to the stimulus frequency which elicited the largest response was normalized to 1. Subsequently, responses were averaged across voxels. On the x-axis, the BF is centered and the distance to non-preferred frequencies are indicated in octave wise steps. Depicted are the median normalized responses and the corresponding 95% confidence intervals. There was no significant difference in cortical frequency tuning between the groups.

is likely to result in larger loudness. Conversely, if the frequency channels themselves have a reduced frequency selectivity, even a narrow-band stimulus will excite more of those channels. Consequently, a tone may be perceived as relatively loud when it excites a large number of frequency channels. In our study, we did not find evidence for a broadening of cortical tuning. Therefore, the increase in perceived loudness in hyperacusis may not be related to a loss of cortical frequency specificity. In line with this, in normal hearing listeners increases in loudness result in increased midbrain activation (Harms and Melcher, 2002; Sigalovsky and Melcher, 2006), even when sound energy is constant. For the primary auditory cortex it has been established that with increased loudness, increased activation is observed in both normal-hearing and hearing-impaired participants (Hall et al., 2001; Langers et al., 2007; Behler and Uppenkamp, 2016). The relation with increased activation is stronger for the loudness than for the intensity of stimuli, and this relation is similar in participants with and without hearing loss. Thus, the relation between loudness and fMRI response amplitude is well established. Hence, the increased responses observed in participants with hyperacusis presumably reflect an increase in the perceived loudness of sounds.

4.3. Central gain and the distinction between loudness recruitment and hyperacusis

In light of the central gain theory, we observed increased activation in response to sound in participants with moderate hearing loss and tinnitus, and the additional presence of hyperacusis. This increased activation was present in both the subcortical auditory structures, and in the primary, secondary, and association auditory cortices. In line with previous findings on hyperacusis, the increased cortical responses were not restricted to the hearing loss area and instead were present for the entire range of frequencies tested (Noreña and Chery-Croze, 2007; Diehl and Schaette, 2015). This frequency independence of loudness perception mirrors the findings of previous studies that reported that the attenuation of high frequencies via earplugging can lead to altered loudness perception in low frequencies (Formby et al., 2003; Munro et al., 2014), and that stimulation at high frequencies decreased the loudness of low frequencies (Noreña and Chery-Croze, 2007). Changes in loudness perception thus appear to affect the entire range of frequencies and are present in areas not directly affected by attenuation or stimulation. This is in line with a report that in patients with hyperacusis complaints the loudness discomfort levels are decreased over the whole range of tested frequencies and not restricted to the hearing loss region (Sheldrake et al., 2015). Therefore, it appears that this heightened reactivity to sound is a phenomenon that occurs separately from loudness recruitment as observed in hearing loss. Whereas in hearing loss steeper growth of loudness is limited to the frequencies where hearing loss is present, in hyperacusis the growth of loudness is present over the whole range of frequencies. In summary, our results show an increase in activation in subcortical and cortical parts of the auditory pathway, where the cortical increase in activation affects the entire frequency range despite hearing loss primarily at high frequencies.

4.4. The cortical response to the tinnitus frequency in the presence of hyperacusis

Stimulation of the auditory cortex with a frequency similar to the tinnitus frequency resulted in a significantly smaller response for the group with hyperacusis. The finding that the brain responds differently to the presentation of the tinnitus frequency in the presence of hyperacusis may indicate that tinnitus with and without hyperacusis reflect different types of tinnitus. Previous work indicates that enhanced responses in the auditory cortex are related to sustained over-attention to the auditory domain (Krumbholz et al., 2007; Paltoglou et al., 2011). It may be that in tinnitus without hyperacusis there is specific over-attention to the tinnitus frequency band, whereas in the presence of hyperacusis attentional resources are drawn by the increased loudness of all sound frequencies. Since both groups in our study experience tinnitus of similar loudness, this suggests that the difference in primary auditory cortex activation in response to the tinnitus frequency is not shaping the tinnitus percept.

Presently, we can only speculate about the cause of the reduced BOLD-response at the tinnitus frequency in hyperacusis. There is currently no research to inform us if external sound stimuli and internal tinnitus activity add up to result in enhanced cortical activation, or whether external stimulation normalizes the tinnitus-related activity. The reduced contrast at the tinnitus frequency observed in the presence of hyperacusis could potentially relate to a saturation effect if the hyperacusis related increase in activity and the response at the tinnitus frequency, as observed in the group without hyperacusis, would add up. This summing of activation could result in a decreased contrast when the activity is already driven to near saturation by the hyperacusis related increase in sound-evoked activity. Alternatively, the presence of hyperacusis related neural hyperactivity in response to sound may cause the external sound to interact with the tinnitus frequency in a different manner than in tinnitus without this subcortical and cortical hyperactivity. Future research will have to inform us about the

precise relation between hyperacusis related neural hyperactivity, a reduction in the response to the tinnitus frequency, and the recruitment of auditory attentional networks.

4.5. The challenge of defining hyperacusis

In the current paper, the definition of hyperacusis is based on the paper of Aazh and Moore (2017), who showed that an HQ cut-off score of 22 matches well with the lower end of the 95% confidence interval identifying patients with reduced loudness discomfort levels (<77 dB HL), thus capturing the majority of patients that present with hyperacusis complaints. Hereby, we deviate from the cut-off score of 28 that was suggested by the developers of the HQ in their original article (Khalfa et al. 2002), which was intended to indicate severe cases of hyperacusis. The original diagnostic criterion of hyperacusis based on an HQ cut-off score of 28 has been challenged (Fackrell et al., 2015; Fioretti et al., 2015; Aazh and Moore, 2017). Apart from the alternative proposed cut-off score of 22 used in the current study, a cut-off score of 16 was proposed by Fioretti et al., (2015) to reflect the presence of hyperacusis based on the comparison of the area under the Receiver Operator Characteristics (ROC) curve of the HQ and uncomfortable loudness levels. However, Sheldrake et al. showed that the use of loudness discomfort levels alone to diagnose hyperacusis results in a large amount of false positives (Sheldrake et al., 2015). Similar to a previous report (Gu et al., 2010), not hyperacusis but tinnitus was the primary complaint of participants in the current study. Please note that patients with severe hyperacusis are unlikely to participate in an fMRI study due to the high sound levels. Our study shows a clear difference in responsiveness of the auditory areas in the group with an HQ-score of 22 and higher compared to those with lower scores. It thus appears that this group, with milder complaints of hyperacusis, can provide us an important window into the subcortical and cortical changes that are related to hyperacusis.

5. Conclusion

Hyperacusis was related to an increase in sound-evoked activity in the subcortical and cortical auditory pathway. For the auditory cortex, this increase was not restricted to the hearing loss frequencies but was present for frequencies outside of the range affected by hearing loss. This result was obtained by comparing two groups, with and without hyperacusis, where both groups had hearing loss and tinnitus. On a subcortical level, hyperacusis was related to higher responses in the MGB, IC, and SOC. On a cortical level, hyperacusis was related to an increase in overall sound-evoked activation in the primary, secondary, and association auditory cortex. We did not identify a hyperacusis related loss of tuning specificity for the primary auditory cortex. In the presence of hyperacusis, responses to the tinnitus frequency were reduced. In summary, higher subcortical and cortical activity in response to sound thus appears to be a marker of hyperacusis.

Declaration of Competing Interest

The authors declare no conflict of interest or competing financial interests.

CRediT authorship contribution statement

E.A. Koops: Conceptualization, Methodology, Software, Data curation, Investigation, Writing - original draft, Visualization. **P. van Dijk:** Conceptualization, Validation, Supervision, Writing - review & editing, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2020.108158.

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