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Research Report

Spontaneous brain activity underlying auditory hallucinations in the hearing-impaired

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ABSTRACT

Auditory hallucinations, the perception of a sound without a corresponding source, are common in people with hearing impairment. Two forms can be distinguished: simple (i.e., tinnitus) and complex hallucinations (speech and music). Little is known about the precise mechanisms underlying these types of hallucinations. Here we tested the assumption that spontaneous activity in the auditory pathways, following deafferentation, underlies these hallucinations and is related to their phenomenology. By extracting (fractional) Amplitude of Low Frequency Fluctuation [(f)ALFF] scores from resting state fMRI of 18 hearing impaired patients with complex hallucinations (voices or music), 18 hearing impaired patients with simple hallucinations (tinnitus or murmuring), and 20 controls with normal hearing, we investigated differences in spontaneous brain activity between these groups. Spontaneous activity in the anterior and posterior cingulate cortex of hearing-impaired groups was significantly higher than in the controls. The group with complex hallucinations showed elevated activity in the bilateral temporal cortex including Wernicke's area, while spontaneous activity of the group with simple hallucinations was mainly located in the cerebellum. These results suggest a decrease in error monitoring in both hearing-impaired groups. Spontaneous activity of language-related areas only in complex hallucinations suggests that the manifestation of the spontaneous activity represents the phenomenology of the hallucination. The link between cerebellar activity and simple hallucinations, such as tinnitus, is new and may have consequences for treatment.

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1. Introduction

The occurrence of auditory hallucinations (AH), the perception of an auditory stimulus in the absence of a corresponding source, is not limited to psychiatric disease (Sommer, Kleijer, & Hugdahl, 2018) Several small-scale studies have suggested a link between hallucinations and deafness (Cole, Dowson, Dendukuri, & Belzile, 2002; Teunisse & Rikkert, 2012). In line with these observations, a recent cross-sectional study including over 1000 subjects reported that between 12% and 24% of patients with hearing loss experience AH, with higher prevalence in more severe hearing impairment (Linszen et al., 2019). The classical form of AH in hearing loss is musical hallucinations, and sometimes musical hallucinations are considered a synonym for hallucinations caused by hearing loss. However, this assumption is not correct, as hallucinations in hearing loss can take many different forms. In fact, the most commonly perceived form of complex hallucinations in hearing-impaired patients is voices (49%), followed by music (36%). Simpler forms of hallucinations, such as bells (24%), also occur in this patient group (Linszen et al., 2019). Tinnitus (a ringing, clicking, buzzing, hissing, or roaring sound) can also be viewed as a simple auditory hallucination, although it is usually not defined as such (Ffytche & Wible, 2014). Patients experience deafferentation hallucinations as a debilitating symptom, leading to impaired quality of life (Coebergh, Lauw, Bots, Sommer, & Blom, 2015). As worldwide auditory impairment is estimated to have doubled by the year 2050, mainly due to increasing age of the population (World Health Organization, 2020), the prevalence of this type of AH can be expected to rise in the next years. Currently, treatment options for both complex and simple hallucinations associated with hearing loss are scarce (Coebergh et al., 2015), unless hearing impairment can be repaired (Colon-Rivera & Oldham, 2014).

While there is ample research dedicated to the underlying mechanisms of AH in schizophrenia, relatively little is known about the neurobiology of AH in the hearing-impaired (Cope & Baguley, 2009). As AH in hearing loss are often non-responsive to antipsychotic medication, increased dopamine synthesis is unlikely to be a contributing factor (Ali, 2002). Rather, similarities in the mechanisms of AH in hearing-impaired persons and that of hallucinations in other sensory modalities with accompanying sensory impairment, such as Charles Bonnet Syndrome occurring in people with visual impairments (De Ridder, Vanneste, & Freeman, 2014) have been noted. This has led to a common theory explaining the occurrence of this type of hallucinations, namely deafferentation (Marschall, Brederoo, Ćurčić-Blake, & Sommer, 2020). For AH in hearing loss, the deafferentation theory suggests that the diminished sensory input from the peripheral auditory system to the higher cortical areas leads to insufficient stimulation of cortical perception areas. As a reaction to this imbalance, the brain tries to reestablish homeostasis by reducing the threshold to detect activity. Consequently, the amount of spontaneous activity detected along the auditory pathways of the brain increases. This spontaneous activity is then misinterpreted as an external auditory stimulus and form the source of the AH (De Ridder et al., 2014; Linszen, Brouwer, Heringa, & Sommer, 2016; Vanneste, Song, & De Ridder, 2013).

Spontaneous brain activity might not only cause the occurrence of deafferentation hallucinations, but could also be involved in the specific phenomenology and complexity of the experience, depending on the location and extent of activity. Neuroimaging studies investigating brain activity in patients with visual deafferentation hallucinations showed that the location of activity corresponds to the phenomenology of the hallucinated images (Ffytche et al., 1998). In this symptom capture study, the patients showed an increase in ventral occipital lobe activity during their visual hallucinations. Activity in more functionally specialized subregions matched characteristics of the hallucination as described by the patients, e.g. increased activity in the left middle fusiform gyrus was found in those patients perceiving faces.

With regard to hearing-impairment, strong support for the deafferentation theory is as of yet lacking. To date, mainly case studies or small-scale studies have investigated brain activity of patients with hallucinations induced by their hearing loss (Cavaliere, Longarzo, Orsini, Aiello, & Grossi, 2018; Futamura, Katoh, & Kawamura, 2014; Griffiths, 2000; Izumi, Terao, Ishino, & Nakamura, 2002; Kumar et al., 2014; Shinosaki et al., 2003; Terao & Matsunaga, 1999; Vitorovic & Biller, 2013). Recruiting larger numbers of patients to generalize findings has proven difficult, perhaps due to a lack of awareness for this type of hallucinations (Marschall et al., 2020).

Spontaneous brain activity in resting state functional magnetic resonance imaging (R-fMRI) has recently been used to study aspects of various psychological and neurological diseases (Hoptman et al., 2010; Liu et al., 2011; Yuan et al., 2013). It is possible to measure the intensity of local spontaneous activity in R-fMRI using a measure called amplitude of low frequency fluctuation (ALFF), i.e., the square root of the power spectrum between .01 and .08 Hz (Zang et al., 2007). This measure reflects the variability of low frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. Within-group changes in ALFF and its fractional counterpart fALFF, i.e., ALFF standardized by its global mean (Zou et al., 2008), resemble for example the default mode network in a healthy population, with fALFF performing better than ALFF(Zou et al., 2008). On the group level, ALFF can be used to detect brain regions that differ in spontaneous activity, while fALFF reveals areas in which the contribution of low frequency amplitudes is elevated (Zuo et al., 2010). As ALFF and fALFF provide complementary information, the two are usually reported together. Interestingly, differences in (f)ALFF have been detected in AH in both schizophrenia patients (Alonso-Solís et al., 2017) and tinnitus patients (Chen, Xia, et al., 2015), indicating an involvement of low frequency fluctuations in other hallucination-like experiences. Based on this information, aberrant (f)ALFF patterns could also be expected in hearing-impaired patients suffering from AH.

Unraveling possible neurobiological underpinnings of AH in hearing-impaired patients is not only an important step towards understanding the underlying mechanisms, but can also be useful in the development of new treatment for this disabling and stressful symptom. Since it has been suggested that the instability of neural networks might be causing the occurrence of hallucinations, non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) or

transcranial direct current stimulation (tDCS) could help to relieve the perceptions by focally reducing network activity and neuronal instability in areas associated with the AH (Banerjee, Sorrell, Celnik, & Pelled, 2017; Matheson, Shemmell, De Ridder, & Reynolds, 2016; Neggers, Petrov, Mandija, Sommer, & van den Berg, 2015; Stagg, Antal, & Nitsche, 2018; Zhao et al., 2017). For such interventions to be successful, information about location of spontaneous over-activity is essential.

The aim of this study is therefore to investigate patterns of spontaneous brain activity in a group of hearing-impaired patients with AH using (f)ALFF. For this purpose (f)ALFF measures of R-fMRI were compared between hearing-impaired patients with complex AH, hearing-impaired patients with tinnitus and/or simple AH and participants without AH. This allowed us not only to investigate changes in spontaneous brain activity underlying AH, but also to study differences depending on complexity and phenomenology of AH.

2. Materials and methods

2.1. Participants

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Eighteen hearing-impaired patients with complex auditory hallucinations [HI–C; 7 male, 11 female; age 33–77 years (mean = 57.78, std = 11.42); 18 suffering from tinnitus] and 18 hearing-impaired patients with simple auditory hallucinations including tinnitus, [HI–S; 6 male, 12 female; age 41–79 years (mean = 58.11, std = 11.99); 16 suffering from tinnitus] were recruited at the audiological center at the University Medical Center Utrecht. All patients suffered from late onset hearing impairment. Hearing impairment was tested using the High Fletcher Index (hFI), that is, the average of unaided air-conduction thresholds at 1000, 2000, and 4000 Hz, of each ear (Teunisse & Rikkert, 2012). Patients were considered to experience complex AH if they described their perception consisting of voices and/or music. Less concrete sounds, such as murmuring or ringing sounds (including tinnitus), were classified as simple hallucinations. This categorization was done based on the most complex AH described by the participants. As a result, there are participants in the HI–C group with a combination of complex and simple hallucinations.

Inclusion criteria for the HI–C group were (1) experience of at least one AH within the past month and (2) hFI $\geq$ 25 dB in the worst ear. Inclusion criteria for the HI–S group were (1) no complex AH within the last two years (or not more than one episode of complex AH longer than two years ago) and (2) hFI $\geq$ 25 dB in the best ear. All patients underwent a semi-structured interview, consisting of 14 items on tinnitus and spontaneous acoustical phenomena, as used by Teunisse and Rikkert (2012). This interview was used to identify the phenomenology of the AH. None of the patients reported the use of any relevant psychotropic medication that might influence the hallucinations, such as antipsychotics. An overview of other psychotropics reported can be found in the supplementary material.

A group of 20 controls with normal hearing [NH; 9 male, 11 female; age 38–65 years (mean = 54.10, std = 7.40)] was recruited. All three groups were matched with respect to age, gender, and handedness. The research was approved by the Local Research Ethics Committee from the University Medical Center Utrecht. All participants gave informed consent before their participation. No part of the study procedures or analyses was pre-registered prior to the research being conducted. The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the lead author prof. I.E.C. Sommer or the local ethics committee at the University Medical Center Utrecht. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must meet the following conditions to obtain the data: completion of a formal data sharing agreement.

2.2. Data acquisition

The resting-state fMRI images (n = 600) were recorded using a 3D-PRESTO pulse sequence with paralleled imaging (SENSE) in two directions sensitive to blood oxygen level dependent (BOLD) contrast [TR = 600 msec, TE = 32.4 msec, 64 mm × 64 mm x 40 mm acquisition matrix, field of view(FOV) = 224 mm × 160 mm, voxel size = 4 mm^3, flip angle 10°, number of slices (coronal) = 40].

High resolution structural T1-weigthed images were collected for anatomical reference (TR = 10 msec, TE = 4.6 msec, FOV = 240 mm/100%, flip angle 90°, 240 × 256 acquisition matrix, voxel size = .75 mm × .75 mm × .80 mm, reconstruction matrix = 200 × 320 x 320).

All structural and functional images were acquired using a Philips Achieva 3.0 T scanner (Philips Medical Systems, Best, The Netherlands) equipped with a commercial 8-channel SENSE head coil. Participants were asked to lie still in the scanner, keep their eyes closed, and to stay awake.

2.3. Data preprocessing

Preprocessing of the R-fMRI data was performed using SPM 12 and the Data Processing & Analysis of Brain Imaging toolbox (DPABI, http://rfmri.org/dpabi). Slice timing and motion correction using the six parameters characterizing head motion were done on all volumes. Following the T1, anatomical images were co-registered to the mean functional images and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) for each participant. During a nuisance regression step the first five principal components of the WM and CSF signal as well as the Friston 24 motion parameters (Friston, Williams, Howard, Frackowiak, & Turner, 1996) were extracted with the CompCor method (Behzadi, Restom, Liau, & Liu, 2007). No global signal regression was performed, instead mean division of the (f)ALFF scores has been implemented at a later stage. This method has been shown to be similar in effectiveness, while also increasing test-retest reliability (Yan, Craddock, Zuo, Zang, & Milham, 2013). Using EPI templates, images were normalized onto

Montreal Neurological Institute space and resampled into 3 mm^3 voxel size. Following this, the data were smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel in order to reduce spatial noise. To reduce the effect of frequency related noise temporal band-pass filtering (.01–.08 Hz) was performed (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Lowe, Mock, & Sorenson, 1998).

2.4. *(f)ALFF calculation*

ALFF and fALFF values were used to uncover differences in local spontaneous brain activity. While ALFF reports differences in spontaneous brain activity compared to baseline, fALFF reveals areas with increased low frequency amplitudes relative to the overall spectrum (Zuo et al., 2010). While the fALFF method has been said to be more specific than the ALFF method by suppressing artifacts and enhancing cortical signals (Zou et al., 2008), it also shows a lower test-retest reliability (Zuo et al., 2010). To ensure specificity as well as reliability of our results we follow the common practice of reporting both measures.

ALFF and fALFF maps for each subject were calculated in the DPABI toolbox (http://rfmri.org/dpabi). To compute the ALFF, the time series of each voxel is transformed into the frequency domain using fast Fourier transform. The square root of the power spectrum is then calculated and the average across .01–.08 Hz is taken. This calculation results in the ALFF at a given voxel (Zang et al., 2007). fALFF is calculated by taking the ratio of power in the low frequency (.01–.08 Hz) relative to the full frequency range (0–.25 Hz). All (f)ALFF values were standardized using mean division. Additional analyses of (f)ALFF scores in the slow 4 (.027–.073 Hz) and slow 5 (.01–.027 Hz) frequency bands have been performed. Their results can be found in the supplementary materials.

2.5. *Statistical analysis*

All analyses of demographic data were implemented in SPSS (Version 25.0). Groups were compared on sex, handedness, and tinnitus (for HI–C and HI–S) using chi-squared tests; differences in age and hearing impairment were assessed with a one-way analysis of variance (ANOVA). While all patients suffered from some level of hearing impairment in both ears, we also addressed the role of the different spectro-temporal processing properties of the left and right auditory system by comparing the level of impairment per side using a two-sample *t*-test and the side of the more severe impairment using a chi squared test. Missing data for 2 HI–C patients on tinnitus occurrence and 1 HI–C on hFI was imputed using group means.

As both ALFF and fALFF are sensitive to signal in gray matter, a grey matter mask was used for further statistical analyses. The grey matter mask was created in SPM 12 using the grey matter image in MNI space provided by the software package. Voxels with a probability of being grey matter of >.2 were included in the mask, resulting in a total of 405,870 voxels in the mask.

All main statistical analyses were performed on both standardized ALFF and fALFF maps. To examine differences between the three groups, an ANOVA was implemented with the hypothesis that all groups are equal. For further differentiation between the groups and control for the predominant side of the impairment, the following post-hoc tests were performed: (1) a two-sample *t*-test comparing NH and a combined HI group (HI–C and HI–S) (2) a two-sample *t*-test comparing HI–C and HI–S (3) a two-sample *t*-test comparing HI–C and HI–S with predominant impairment on the right side and (4) a two-sample *t*-test comparing HI–C and HI–S with predominant impairment on the left side. All tests were done using non-parametric permutation testing in the SnPM toolbox (SnPM13; http://warwick.ac.uk/snpm) with n = 10,000 permutations and 10 mm variance smoothing. For all tests cluster-wise inference was used, with the a priori cluster defining threshold set to an equivalent of $p = .001$ (Woo, Krishnan, & Wager, 2014). All main analyses were performed using family-wise error (FWE) correction with statistical significance at $p_{FWE} < .05$ level.

3. Results

3.1. *Demographic data*

The groups did not differ significantly with regard to age [$F(2,53) = .888$, $p = .417$], sex ($\chi^2 = .542$, $p = .762$), or handedness ($\chi^2 = 4.01$, $p = .405$). Further post hoc comparisons between HI–C and HI–S showed no significant differences in age [$t(34) = .221$, $p = .641$], sex ($\chi^2 = .120$, $p = .729$), or handedness ($\chi^2 = 2.933$, $p = .231$) either. Comparisons between the two hearing impaired groups showed no significant group differences in hFI for both the worst [$t(34) = -.285$, $p = .777$] and the best ear [$t(34) = -.119$, $p = .910$]. There were no significant differences between the hFI on either the left [$t(34) = -.762$, $p = .451$] or the right [$t(34) = .537$, $p = .595$] side in the two HI groups. These two groups also showed no significant differences in the distribution the side of more severe impairment ($\chi^2 = .038$, $p = .981$), of tinnitus ($\chi^2 = 2.118$, $p = .146$), the perception of murmur ($\chi^2 = .148$, $p = .700$), and the perception of bells ($\chi^2 = .364$, $p = .546$) (see Table 1).

3.2. *ALFF*

The ANOVA of the ALFF maps comparing the three groups, HI–C, HI–S, and NH, showed a significant difference across these groups in a cluster of k = 1825 voxels ($p_{FWE} = .002$) with a peak in the left precuneus ($t = 9.37$; see Table 2).

Post-hoc comparison using a two-sample *t*-test between NH and the combined HI group is visualized in Fig. 1. It shows that HI patients have significantly higher ALFF scores than NH in two clusters. The first cluster is located in the left temporal lobe (k = 79, $p_{FWE} = .022$) with a peak at the left parahippocampal gyrus ($t = 5.22$). The second cluster (k = 180, $p_{FWE} = .002$) shows bilateral peaks in the anterior part of the cingulate cortex ($t = 4.29$). Significant lower ALFF scores were found in one cluster (k = 131, $p_{FWE} < .015$) with peaks in the left middle occipital gyrus ($t = 4.14$) and the left precuneus ($t = 4.12$; see Table 2).

Further post hoc comparison of ALFF scores between HI–C and HI–S using a two-sample *t*-test resulted in no surviving clusters.

Table 1 – Comparison of the demographic variables per group.

		NH	HI–S	HI–C	Significance	
		n = 20	n = 18	n = 18	3 groups	HI–C versus HI–S
Age	Mean (SD)	54.10 (7.40)	58.11 (11.41)	57.78 (11.99)	.417	.641
Sex	Male (%)	45	33.3	38.9	.762	.298
	Female (%)	55	66.7	61.1		
Handedness	Right (%)	85	77.8	88.9	.405	.231
	Left (%)	15	22.2	5.6		
	Both (%)	0	0	5.6		
hFI worst ear	Mean (SD)	–	63.24 (27.61)	60.83 (22.65)	-	.777
hFI best ear	Mean (SD)	–	44.61 (18.08)	43.80 (22.50)	-	.910
hFI left	Mean (SD)	–	55.78 (31.95)	48.80 (22.18)	-	.451
hFI right	Mean (SD)	–	52.06 (15.33)	55.83 (25.59)	-	.595
More severe impairment[a]	Right (%)	–	44.4	41.2	–	.981
	Left (%)	–	50.0	52.9	–	
	Both (%)	–	5.6	5.9	–	
Tinnitus[b]	Present (%)	–	88.9	100	-	.146
Murmuring[b]	Present (%)	–	22.2	27.9	–	.700
Bells[b]	Present (%)	–	6.6	11.1	-	.546
Music[b]	Present (%)	–	–	72.2	-	-
Voices[b]	Present (%)	–	–	44.4	-	-

HI–C = hearing impaired with complex hallucinations; HI–S = hearing impaired with simple hallucinations; NH = controls with normal hearing.
[a] Side on which the hFI was worse, both indicates same score on each side.
[b] Combinations of these categories were possible.

Table 2 – Results of the ANOVA comparing the ALFF maps of the three groups including post-hoc comparisons between the combined hearing-impaired (HI) group and the controls with normal hearing (NH)) as well as the post-hoc comparison between the complex (HI–C–l) and simple (HI–C–l) hearing-impaired groups with worse impairment on the left ear.

Contrast	Cluster	k[a]	Activation Locus	BA[b]	SnPM{t}	Local maxima[c]		
						x	y	z
HI > NH	1	79	L Parahippocampal gyrus	36	5,22	−24	−3	−42
	2	180	R Ventral Anterior Cingulate gyrus	24	4,28	0	21	24
			L Dorsal Anterior Cingulate gyrus	32	3,99	−9	27	27
HI < NH	1	131	L Middle Occipital gyrus	18	4,14	−21	−90	3
			L Precuneus	7	4,12	−24	−75	30
HI–C–L < HI–S–L	1	63	L Paracentral Lobule	1	4,77	−9	−36	78
			R Supplementary Motor Cortex	6	4,55	3	−27	75

[a] Cluster size in voxels.
[b] Brodmann area.
[c] Coordinates in MNI space.

While the post-hoc comparison of ALFF scores between HI–C and HI–S based on the predominant side of impairment resulted in no surviving clusters for the right side, there was an increase in ALFF scores in the HI–S group with impairment on the left side as compared to the HI–C group with impairment on the left side. The cluster (k = 63, p_{FWE} = .045) is located at the left paracentral lobule and the right supplementary motor cortex (t = 4.77; t = 4.55; see Table 2).

3.3. *fALFF*

Group comparison using ANOVA showed significant differences across the three groups, HI–C, HI–S, and NH, in a cluster of k = 1480 voxels (p_{FWE} = .002), with peaks at the left posterior cingulate cortex (t = 18.72) and the left lingual gyrus (t = 15.35; see Table 3).

As seen in Fig. 2 post hoc comparison of fALFF scores between NH and the combined HI group-using a two-sample t-test, resulted in three clusters of increased fALFF scores in HI patients (k = 168, p_{FWE} < .001; k = 63, p_{FWE} = .025; k = 61; p_{FWE} = .027). Peaks of the first cluster were found in the left posterior cingulate cortex (t = 5.56). The second cluster peaked in the right posterior cingulate cortex (t = 3.61). For the third cluster peaks were located in the left lingual gyrus (t = 3.95). No significantly lower fALFF scores in HI were observed when correcting for FWE.

The post hoc two-sample t-test comparing HI–C and the HI–S group shows a significant increase in fALFF scores in the HI–C group in five clusters (see Fig. 3). The first cluster (k = 7036; p_{FWE} < .001) peaked at the left inferior temporal gyrus (t = 15.53, see Table 2) and the left cuneus (t = 9.92). Another cluster (k = 2991; p_{FWE} = .006) was found with peak

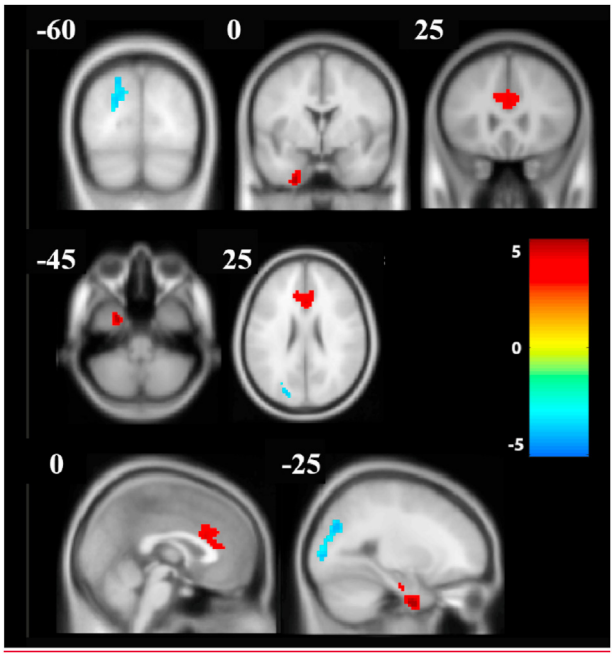

Fig. 1 – ALFF maps comparing the combined hearing-impaired (HI) group with controls with normal hearing (NH). Warm indicates areas with increased ALFF scores in HI compared to NH, cold indicates areas with decreased ALFF scores in HI compared to NH. The colorbar represents SnPM pseudo-T values.

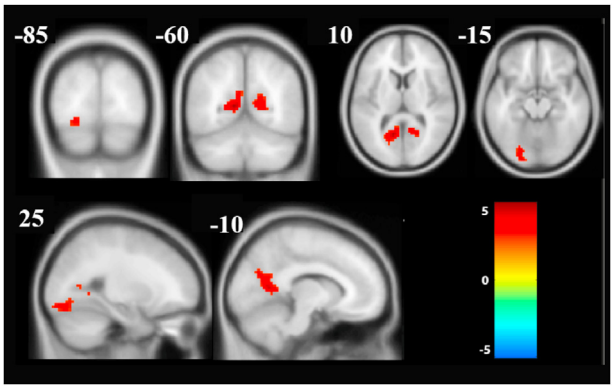

Fig. 2 – fALFF maps comparing the combined hearing-impaired (HI) group with controls with normal hearing (NH). Warm indicates areas with increased fALFF scores in HI compared to NH, cold indicates areas with decreased ALFF scores in HI compared to NH. The colorbar represents SnPM pseudo-T values.

at the right inferior temporal gyrus (t = 10.28). The third cluster (k = 610; p_{FWE} = .001) is located at the frontal lobe and peaks in the left rectal gyrus and orbital gyrus (t = 8.66; t = 8.52). Furthermore, a cluster (k = 1761; p_{FWE} < .001) with peak at the left precentral gyrus and insula (t = 4.87; t = 3.94) was found to be significant. The last cluster (k = 102; p_{FWE} = .033) in which the two groups differ shows peaks in the middle and superior temporal gyrus (t = 4.87; t = 3.94) including Wernicke's area.

Significantly lower fALFF scores in HI–C than in HI–S patients were found in one cluster (k = 9385; p_{FWE} < .001) with peaks in the cerebellum and the brainstem area. As the large size of the clusters limit the specificity of these results an additional voxel level analysis has been performed. The results include the cerebellum, brainstem, anterior cingulate cortex, temporal pole, and putamen. This analysis can be found in the Supplementary material.

The post-hoc comparison of fALFF scores between HI–C and HI–S based on the predominant side of impairment

Table 3 – Results of the ANOVA comparing the (f)ALFF maps of the three groups including post-hoc comparisons between the combined hearing-impaired (HI) group and the controls with normal hearing (NH), as well as the hearing-impaired patients with complex (HI–C) and the simple (HI–S) hallucinations.

Contrast	Cluster	k[a]	Activation Locus	BA[b]	SnPM{t}	Local maxima[c]		
						x	y	z
HI > NH	1	168	L Ventral posterior cingulate cortex	23	5,56	−12	−60	9
	2	63	L Dorsal posterior cingulate cortex	31	3,61	−6	−60	21
			R Ventral posterior cingulate cortex	23	4,55	15	−57	9
	3	61	L Lingual gyrus	18	3,95	−24	−81	−15
HI–C > HI–S	1	7036	L Inferior Temporal gyrus	20	15,53	−60	−27	−33
			L Cuneus	19	8,92	−24	−90	33
	2	299	R Inferior Temporal gyrus	20	10,28	57	−18	−39
	3	610	L Rectal Gyrus	11	8,66	−3	24	−30
			L Orbital gyrus	47	8,52	−12	27	−30
	4	1761	R Precentral	6	7,33	36	−6	45
			R Insula	13	6,16	39	−9	21
	5	102	R Middle Temporal gyrus	21	4,87	66	−42	0
			R Superior Temporal gyrus	22	3,94	69	−39	12
HI–C < HI–S	1	9385	L Cerebellum		10,41	−12	−36	−24
HI–C–L < HI–S–L	1	67	L Inferior Parietal Lobule	7	4,11	−27	−69	54
			L Angular gyrus	39	3,99	−42	−54	51

[a] Cluster size in voxels.
[b] Brodmann area.
[c] Coordinates in MNI space.

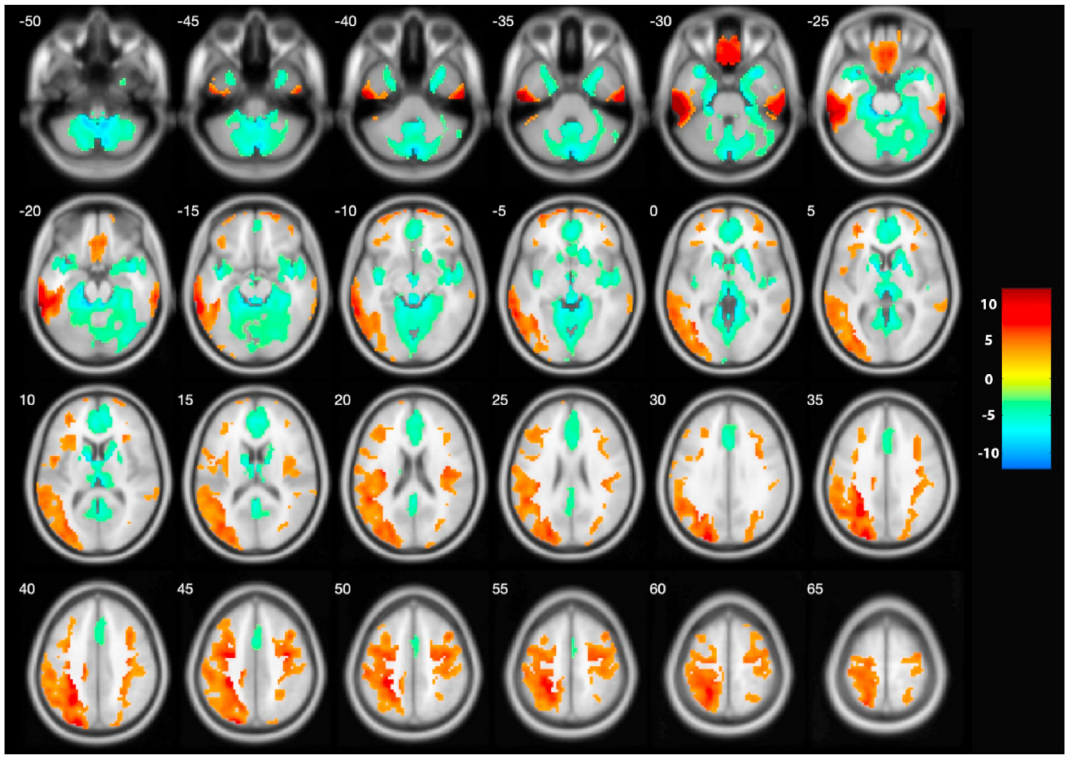

Fig. 3 – fALFF maps comparing the hearing-impaired patients with complex (HI–C) and simple (HI–S) hallucinations. Warm indicates areas with increased fALFF scores in HI–C, cold indicates areas with decreased ALFF scores in HI–C. The colorbar represents SnPM pseudo-T values.

resulted in no surviving clusters, for the right side. For the left side fALFF scores in the HI–S group with impairment on the left side was increased as compared to the HI–C group with impairment on the left side. The cluster ($k = 67$, $p_{FWE} = .032$) is located at the left inferior parietal lobule and the left the left angular gyrus ($t = 4.11$; $t = 3.99$; see Table 3).

4. Discussion

We investigated spontaneous brain activity in three different groups: hearing impaired patients with either complex (HI–C) or simple (HI–S) hallucinations, as well as controls with normal hearing (NH). Our results show that hearing-impaired individuals with any form of hallucinations show increased spontaneous activity in areas known to be involved in hallucinations, such as the anterior cingulate cortex (ACC) and the parahippocampal gyrus (as indicated by ALFF scores) as well as in the posterior cingulate cortex, (PCC; as indicated by fALFF scores), areas known for higher order cognitive processes, such as attention, salience and memory.

While the two patient groups did not differ in their ALFF scores, fALFF scores revealed that patients with complex hallucinations showed more spontaneous activity in areas related to language comprehension, whereas in the group with simple hallucinations activity was found predominately in the cerebellum.

4.1. *Spontaneous activity in higher order cognitive areas underlies hallucinations*

The increased spontaneous activity in the ACC as seen in both patient groups can be linked to this area's involvement in attention and salience detection (De Ridder et al., 2014), possibly indicating a heightened awareness of perceived sound. Notably, the ACC plays an important role in the comprehension of and attention to auditory stimuli (Giraud et al., 2004). As part of the salience network it is mainly involved in the processing of external stimuli, but has also been shown to contribute to filling in auditory information (Shahin, Bishop, & Miller, 2009). Recent findings have suggested that this involvement of the ACC might be connected to a lack of top-down noise-cancelling mechanisms (Vanneste, Alsalman, & De Ridder, 2019) and deviances in error monitoring (Bush, Luu, & Posner, 2000), consistent with theories of AVH (Aleman, Böcker, Hijman, de Haan, & Kahn, 2003; Hugdahl, 2009; Northoff, 2014) indicating the possibility of a mixture of top-down involvement in the perception of the sound.

Further evidence pointing towards higher attention to the hallucination are represented in increased spontaneous activity levels in the PCC of the hearing-impaired individuals as compared to controls. The PCC has been linked to selective attention towards auditory verbal stimuli (Leminen et al., 2019) as well as listening to degraded, difficult to comprehend speech (Obleser, Wise, Dresner, & Scott, 2007). This area is

known to be responsible for internally directed attention (Leech & Sharp, 2014) and has been associated with AH in schizophrenia (Shinn, Baker, Cohen, & Öngür, 2013). Interestingly, heightened activity in the PCC has also been reported in non-clinical populations experiencing AVH (van Lutterveld, Diederen, Otte, & Sommer, 2014). In parallel, to our findings, a case study by Kumar et al. (2014) demonstrated an association between the PCC and musical hallucinations.

As deafferentation and the underlying sensory impairment is often said to cause uncertainty in perception, it is assumed that patients can overcome this uncertainty by facilitating their memory to fill in missing information (De Ridder et al., 2014). This process has been thought to be regulated by the parahippocampus, due to its central role in encoding sensory information from the auditory system into the long-term memory and vice versa (Engelien et al., 2006). In line with this, our patient groups showed an increase in ALFF scores in this area compared to the control group. Indeed, dysfunction of the parahippocampal areas have been described in the context of hallucinations, including patients suffering from schizophrenia (Diederen et al., 2010; Shergill et al., 2003) and tinnitus (Chen et al., 2017; Vanneste, Joos, & De Ridder, 2012).

4.2. *Increased temporal lobe activity in complex as compared to simple hallucinations*

To our knowledge only one study (Vanneste et al., 2013) investigated brain activity of hearing-impaired patients with complex musical hallucinations and compared that to hearing-impaired patients with tinnitus in two groups of 10 patients. Similar to our results they differentiated musical hallucinations from tinnitus based on temporal lobe activity. The whole temporal gyrus has been shown to be critical for multimodal and modality-specific language processing (Jackson, Bajada, Rice, Cloutman, & Lambon Ralph, 2018; Price, 2010). This increase in temporal lobe activity suggests an involvement of bottom-up compensatory processes in complex AH (Mohan & Vanneste, 2017). In accordance with the present results, previous case studies showed that increased activity in temporal areas (Bernardini, Attademo, Blackmon, & Devinsky, 2017; Bleich-Cohen, Hendler, Pashinian, Faragian, & Poyurovsky, 2011; Calabrò et al., 2012; Jang et al., 2011; Kumar et al., 2014), especially, areas close to the superior temporal are associated with musical hallucinations.

Furthermore, our findings include other critical regions for speech comprehension, such as Wernicke's area (Ardila, Bernal, & Rosselli, 2016) which has frequently been associated with auditory verbal hallucinations in psychotic populations (Stephane, Barton, & Boutros, 2001; Upthegrove et al., 2016; Ćurčić-Blake et al., 2013) and the precentral gyrus, an area associated with inner speech in patients suffering from hallucinations (Shergill et al., 2003) as well as AVH in both healthy and psychotic individuals (Diederen et al., 2012).

4.3. *The role of the cerebellum and attention in simple hallucinations*

As for the comparison between the HI–C and HI–S groups, the spontaneous activity in the cerebellum differs strikingly with increased spontaneous activity scores in the HI–C group. While the cerebellum is traditionally considered a motor area, there is evidence for role of the cerebellum in auditory processing (Baumann & Mattingley, 2010; Petacchi, Kaernbach, Ratnam, & Bower, 2011). Interestingly, increases in cerebellum activity are frequently reported in studies investigating tinnitus (Chen et al., 2017; Maudoux et al., 2012; Ueyama et al., 2015). In line with this, hyperactivity within the cerebellum has been observed in animal models of tinnitus, leading to a cerebellar-tinnitus gating hypothesis (Bauer, Kurt, Sybert, & Brozoski, 2013; Brozoski, Ciobanu, & Bauer, 2007; Chen, Zhang, et al., 2015). Our findings support this hypothesis in showing that individuals who experience simple hallucinations (such as tinnitus and murmuring) are characterized by increased cerebellar activity, when compared to individuals who experience more complex hallucinations. An association between the cerebellum and tinnitus is in line with earlier findings indicating that the cerebellum compares afferent signals of the cochlea with higher order information of the auditory cortex (Chen, Xia, et al., 2015).

Additionally, increases in fALFF scores in both the putamen and the anterior cingulate cortex in the tinnitus group as compared to the HI–C group point towards issues with the selection and gating mechanism for auditory attention (Frank, Santamaria, O'Reilly, & Willcutt, 2007; Humphries, Stewart, & Gurney, 2006) in this group. As the putamen plays an important role in the regulation and integration of perception (Buckner et al., 2009) it is possible that these deviations on spontaneous activity sustain the experience of tinnitus and more simple hallucinations.

4.4. *Deafferentation or misinterpretation of internal stimuli?*

Based on the deafferentation theory, we would have expected to find a continuum from normal hearing via simple AH towards complex AH, with increasing levels of spontaneous activity either along the auditory pathway or in areas of higher order auditory processing AH (De Ridder et al., 2014; Linszen et al., 2016; Vanneste et al., 2013). Indeed, the main difference between controls and hearing-impaired patients reflects higher order processes of auditory perception which could resemble more general mechanisms of hallucinations. These differences involve areas known for their role in attention, memory, and error monitoring (Bush et al., 2000; De Ridder et al., 2014; Engelien et al., 2006). Regarding deafferentation, these deviations in attention and error monitoring might point towards a lowered detection threshold for spontaneous activity. Since there are no significant differences in spontaneous activity between the control and the patient group along lower level areas of the auditory pathway, our results suggest that there are similar basal activity patterns that are interpreted differently on a higher (cortical) level, such as a lowered threshold to detect activity. While this could explain the occurrence of deafferentation hallucinations, the differences in spontaneous activity in auditory areas, as found comparing the two patient samples, could explain the phenomenology of the hallucination. Similar to the study by Ffytche et al. (1998) our patient groups showed differences in sensory areas corresponding to the

sound they perceived. Based on this, deafferentation might be a combination of higher order deviations causing a stronger activity detection which in turn leads to a misinterpretation of spontaneous activity in lower level auditory pathway.

While (f)ALFF is often seen as spontaneous neuronal activity (Zang et al., 2007; Zou et al., 2008), this measure can also be interpreted in with regard to its temporal properties. A recent theory, namely spatiotemporal psychopathology (Northoff & Duncan, 2016), has suggested deviations in this variability could also be associated with changes in the integration of inner and outer stimuli. The temporal shift due to the diversions of the (f)ALLF scores might result in a disbalance of the way different regions or networks integrate stimuli (Northoff 2018). This has been shown to cause changes in perception, like abnormal speed perception (Northoff et al., 2018). As our results show increased variability in the anterior and posterior cingulate cortex, two areas associated with self-referential processing (Northoff et al., 2006), in the HI groups, they might experience an over-representation of self-referential thoughts and attention. This in turn might cause them to misinterpret internally generated sounds due to deviations in the auditory cortex as externally located. For future studies an investigation of temporal binding, i.e., functional connectivity analyses between these regions could bring new insights into this possible explanation and distinguish it from deafferentation.

4.5. *Implications for treatment*

Currently, treatment options for deafferentation hallucinations are limited. While the improvement of a patient's hearing abilities can be successful in relieving hallucinations (Coebergh et al., 2015; Sommer, Roze, Linszen, Somers, & van Zanten, 2014), this is often not feasible. Based on the underlying mechanisms, behavioral interventions, like distracting patients from their hallucinations with more salient stimuli, could provide temporary relief. Indeed, distractors, such as listening to music or stories, have been successful in momentary lowering the burden of the hallucinations (Coebergh et al., 2015). An alternative treatment option could be non-invasive brain stimulation, using tools like rTMS or tDCS (Neggers et al., 2015; Stagg et al., 2018). Here we presented several brain areas that could be used as treatment targets. Based on the phenomenology of the hallucination, a downregulation of spontaneous activity in the temporal lobe for complex AH or the left cerebellum for simple AH could be beneficial. Both areas have been shown suitable targets for neurostimulation (Moseley et al., 2014, 2016; van Dun, Bodranghien, Manto, & Mariën, 2017) and protocols similar to those used in AVH in schizophrenia (Otani, Shiozawa, Cordeiro, & Uchida, 2015) could be applied. As for tinnitus, both rTMS and tDCS have shown promising treatment outcomes (Soleimani, Jalali, & Hasandokht, 2016; Yuan, Yadollahpour, Salgado-Ramírez, Robles-Camarillo, & Ortega-Palacios, 2018). Following a study by Plewnia, Bartels, and Gerloff (2003), rTMS is usually applied to the left temporal lobe. Nonetheless, there is no agreement on the best treatment location as of yet (Soleimani et al., 2016). However, further investigation is needed.

4.6. *Limitations*

The scope of this study was limited in terms of assessing the exact nature of the hallucinations. While all patients confirmed that they frequently experience hallucinations in daily life, we cannot assure the actual occurrence of hallucinations during the MRI scan as we did not use a button-press protocol. Instead of investigating the actual moment a hallucination takes place, we rather studied hallucinations as a trait. For this reason, it is difficult so ensure a direct relationship between the spontaneous activity and the hallucination as a state.

In individuals who experience hearing impairment, tinnitus is a common phenomenon regardless whether they perceive additional complex auditory hallucinations or not (Linszen et al., 2019). Concordantly, tinnitus was reported by individuals in the complex hallucination group as well, in addition to being a characterizing feature of the simple hallucination group. As such, singling out the mechanism underlying tinnitus was not possible in the present study, as our sample did not allow for a differentiation between the two hearing-impaired groups based on the occurrence of tinnitus.

While all patients in this study suffer from late onset hearing impairment, we lack information on the exact cause and duration of their impairment. Since the possible causes of hearing impairment are vast (Cunningham & Tucci, 2017), it is likely that differences in these factors might be related to the phenomenology of the hallucination, such as the complexity of the hallucination.

Using both ALFF and fALFF led to different results in our sample. As these are different measures, different outcomes are possible and have been reported in previous studies (Cui et al., 2014; Lv et al., 2014). Given the higher sensitivity of fALFF compared to ALFF it is not surprising that we found stronger differences using this measure, however these results might be less stable (Zou et al., 2008; Zuo et al., 2010).

4.7. *Conclusion*

The deafferentation theory, commonly used to explain the occurrence of hallucinations in sensory impairment, suggests an increase in spontaneous brain activity along the sensory pathways, as well as a lowered threshold to detect this activity (Marschall et al., 2020). Here we tested this theory for the first time in a large sample using resting-state fMRI. Consistent with this theory our three groups (controls with normal hearing, hearing-impaired individuals with complex hallucinations, and hearing-impaired individuals with simple hallucinations) can be differentiated based on patterns of their spontaneous brain activity.

While the difference in areas such as the anterior and posterior circulate cortex between controls and the hearing-impaired might underlie more general aspects of auditory hallucinations, such as differences in attention and salience, as well as problems with error monitoring, the distinction between complex and simple hallucinations gave us insights into the mechanisms underlying the phenomenology of the hallucinations. Interestingly, the two hearing impaired groups differed strongly in spontaneous activity, with the simple hallucinations involving the cerebellum, known to play a

substantial role in tinnitus-like and simple hallucinations. Regarding complex hallucinations, bilateral temporal areas were involved, providing evidence for a relation between phenomenology and locus of spontaneous activation, furthering the idea of a deafferentation mechanism. Yet, alternative explanations, like the misallocation of internally created stimuli should be considered and tested in the future.

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Author contributions

Conceptualization: TMM, BCB, and IECS; Methodology: TMM, BCB, RJR, and IECS; Formal Analysis: TMM; Investigation: MMJL and SK; Data Curation: MMJL and SK; Writing – Original Draft: TMM; Writing – Review & Editing: TMM, BCB, SB, RJR, MMJL, SK, and IECS; Supervision: BCB, SB, RJR, and IECS; Funding Acquisition: IECS.

Declaration of Competing Interest

No conflicts of interest.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2020.12.005.

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