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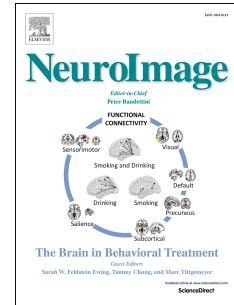
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# Accepted Manuscript

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# 1 **Neuroanatomical substrate of noise sensitivity**

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**Abstract**

Recent functional studies suggest that noise sensitivity, a trait describing attitudes towards noise and predicting noise annoyance, is associated with altered processing in the central auditory system. In the present work, we examined whether noise sensitivity could be related to the structural anatomy of auditory and limbic brain areas. Anatomical MR brain images of 80 subjects were parcellated with FreeSurfer to measure grey matter volume, cortical thickness, cortical area and folding index of anatomical structures in the temporal lobe and insular cortex. The grey matter volume of amygdala and hippocampus was measured as well. According to our findings, noise sensitivity is associated with the grey matter volume in the selected structures. Among those, we propose and discuss particular areas, previously linked to auditory perceptual, emotional and interoceptive processing, in which larger grey matter volume seems to be related to higher noise sensitivity.

34

**Keywords**

Anatomical MRI, auditory cortex, hippocampus, noise sensitivity, right anterior insula

## 37 Introduction

38 Noise, described as an any unwanted sound irrespective to its physical properties, can  
39 adversely affect our well-being. A large body of research links noise to general disturbance,  
40 sleep problems, cognitive impairments and cardiovascular diseases (for reviews, Basner et al.,  
41 2014; Stansfeld and Matheson, 2003). Nevertheless, susceptibility to the negative health  
42 effects of noise differs among people. One of the indicators of the vulnerability to the  
43 environmental noise is *noise sensitivity*. Noise sensitivity describes a stable individual trait  
44 that determines a general attitude towards noise (Stansfeld, 1992). According to the  
45 definition of Job (1999), it refers to physiological and psychological (also including  
46 attitudinal) internal states of any individual, which determines reactivity to noise. Noise  
47 sensitivity predicts noise annoyance (Stansfeld, 1992; van Kamp et al., 2004), and it influences  
48 one's evaluation of the soundscape's pleasantness (Lindborg and Friberg, 2016). Moreover,  
49 noise sensitivity moderates one's daily behaviour; for instance, noise-sensitive individuals  
50 rarely have music in the background (Kliuchko et al., 2015) and often use hearing protection  
51 at work (Heinonen-Guzejev et al., 2011).

52 Noise sensitivity has not been linked to the acuity of peripheral hearing, intensity  
53 discrimination, or auditory reaction time (Ellermeier et al., 2001; Heinonen-Guzejev et al.,  
54 2011; Stansfeld et al., 1985). However, it is shown to be related to the mechanisms of the  
55 central sound processing (Kliuchko et al., 2016; Shepherd et al., 2016). Noise sensitivity is also  
56 correlated with annoyance induced by noise (Heinonen-Guzejev, 2008), which suggests that  
57 noise-sensitive individuals develop affective reaction towards noise easier than noise-  
58 resistant individuals. Some authors suggested that noise sensitivity is a part of a general  
59 predisposition of an individual to experiencing negative emotions towards events, sensations  
60 and self (Watson and Clarck, 1984) as well as exhibiting increased responses to stress and

61 discomfort (Persson et al., 2007; Weinstein, 1978). In the present study, we aimed at  
62 investigating whether morphological variations in the structure of auditory and non-auditory  
63 brain areas dedicated to sensory-emotional processing and evaluation of auditory  
64 information could be related to noise sensitivity.

65 Recent electrophysiological studies have associated noise sensitivity with neural deficits in  
66 central auditory function, advocating for a perceptual/sensory component to noise sensitivity.  
67 As such, highly noise-sensitive individuals were found to exhibit altered sensory gating  
68 (Shepherd et al., 2016) and pre-attentive discrimination of sound noisiness (Kliuchko et al.,  
69 2016). These functional changes could be paralleled by anatomical differences in the central  
70 auditory structures. The relation between function and structure of auditory areas is found,  
71 for instance, in autistic patients. They are reported to have reduced volume of the planum  
72 temporale (Rojas et al., 2002), which is involved with segregation and matching  
73 spectrotemporal auditory information (Griffiths and Warren, 2002). Poor abilities in  
74 segregating relevant acoustic signals, in turn, are related to the sound intolerance that is  
75 exhibited in autistic patients (Lodhia et al., 2014). If noise sensitivity is related to deficits in  
76 the auditory processing, we could expect a negative relationship between noise sensitivity  
77 and the size of auditory cortical areas. On the other hand, their enlargement could mean an  
78 involvement of wider areas into sound processing that could result in hypersensitivity to  
79 sounds.

80 However, auditory areas of the temporal lobe are not the only structures that contribute to  
81 the processing of the auditory signal. Subcortical amygdala and hippocampus are responsive  
82 to physical features and regularity of sensory input. For instance, animal studies (Bordi and  
83 LeDoux, 1992) and human functional magnetic resonance imaging (fMRI) (Kumar et al., 2012)  
84 showed that amygdala encodes acoustical cues that are relevant to the evaluation of

85 emotional valence. A sustained amygdala activation can be evoked by unpredictable auditory  
86 stimulation, and this activation is coupled with anxiety-like behaviours (Herry et al., 2007).  
87 The hippocampus is also involved on auditory information processing and contributes to  
88 sensory gating, which is an inhibition of irrelevant, repetitive sensory input (Cromwell et al.,  
89 2008). Moreover, the amygdala-hippocampal complex displays a unidirectional coupling  
90 during processing of emotionally important stimuli, so that amygdala detects a stimulus'  
91 salience and then influences dynamics of the hippocampal response to it (Zheng et al., 2017).  
92 In turn, hippocampus-dependent memory representations of stimulus emotional significance  
93 can influence amygdalar function (Phelps, 2004).

94 Both the hippocampus and amygdala have rich connections with auditory areas of the brain.  
95 Amygdala receives inputs from the auditory cortex and less processed information directly  
96 from the thalamus. Through its connections to the inferior colliculus, the amygdala may  
97 potentially influence the processing of an auditory stimulus even before it reaches the cortex  
98 (Marsh et al., 2002). The hippocampus, in turn, does not have direct connections with the  
99 primary and secondary auditory cortical areas (Mohedano-Moriano et al., 2007), but it is  
100 largely interconnected with auditory associative areas either directly or via pathways coming  
101 through the amygdala, insula, and other cortical areas, such as the temporal pole (Pascual et  
102 al., 2015). The hippocampus responds to sounds or the sound deprivation (e.g., in hearing  
103 loss) with the neuroplastic changes in its functional and structural organization (Kraus and  
104 Canlon, 2012). Moreover, the volume of amygdala and hippocampus is known to decrease in  
105 chronic stress (Abdalla and Geha, 2017), and small hippocampus is predictive for pathological  
106 stress responses (Gilbertson et al., 2002). In relation to noise sensitivity, an increase and  
107 decrease in amygdalar and hippocampal volumes could be expected alike. A larger volume of  
108 these structures could indicate increased activation of amygdala during sound processing,

109 from which an enlargement of both amygdala and hippocampus could follow, as they are  
110 functionally tight. In turn, a decrease in volume of hippocampus and amygdala could result  
111 from emotional stress noise-sensitive people experience in response to noises.

112 In addition to the auditory cortex, amygdala, and hippocampus, an important role in stimulus  
113 evaluation is played by insula. A recent study found that the insula is related to symptoms of a  
114 distress caused by tinnitus but not to the characteristics of tinnitus itself, such as its loudness  
115 (Leaver et al., 2012). Further, in misophonia (an affective disorder characterized by negative  
116 emotions towards specific sounds, such as chewing or swallowing) the activation of bilateral  
117 anterior insula increased parallelly with higher subjective misophonic distress caused by a  
118 triggering sound (Kumar et al., 2017). Other studies propose that anterior insula is involved in  
119 anticipation of aversive bodily states and negative emotions (Phelps et al., 2001). Moreover,  
120 insula, along with the amygdala and the hippocampus, can have an influence on autonomic  
121 functions. Shepherd and colleagues (2016) observed differences in the dynamics of heart rate  
122 in response to emotional stimuli and heart rate variability between noise-sensitive and noise-  
123 resistant groups. Changes in heart rate serve as indices of noise sensitivity affecting  
124 integration between central and autonomic nervous systems (Thayer and Lane, 2000). Hence,  
125 we expected that noise sensitivity could be related to the structure of the insular cortex that is  
126 involved in regulating autonomic functions and plays a major role in the interoceptive feeling.  
127 As the insular cortex and, specifically, its anterior part was found enlarged in relation to  
128 distress caused by sound sensitivities, such as tinnitus and misophonia (Leaver et al., 2012),  
129 we could expect the same pattern of structural change to occur in relation to noise sensitivity.

130 In this study, we measured grey matter volume and morphology (cortical area, cortical  
131 thickness and cortical folding) in selected regions of interest from both cerebral hemispheres,  
132 namely auditory regions, hippocampus, amygdala, and insula, using FreeSurfer package for an



133 automatic parcellation and labelling of cortical and subcortical structures (Dale et al., 1999;  
134 Fischl et al., 1999). These measures were used to explore whether noise sensitivity is related  
135 to changes in the brain morphology and what the direction of that relationship is.

## 136 **METHODS**

### 137 **Participants**

138 The experimental procedure for this study was included in the research protocol “Tunteet”  
139 (Emotions), which was approved by the Coordinating Ethics Committee of the Hospital  
140 District of Helsinki and Uusimaa. All experiments were conducted in agreement with the  
141 ethical principles of Declaration of Helsinki. Subjects were recruited through email lists of the  
142 University of Helsinki. The inclusion criteria consisted of MRI safety considerations as well as  
143 the absence of hearing, neurological and psychiatric problems. All participants gave their  
144 written consent to participate in the study prior to the experiment. They were compensated  
145 for their time spent in the laboratory, traveling and filling questionnaires online by culture  
146 vouchers.

147 From the “Tunteet” dataset we selected those participants that underwent anatomical MR  
148 scanning and whose images were successfully parcellated with FreeSurfer (N=121). Two of  
149 them were excluded from the analysis due to brain abnormalities detected by a  
150 neuroradiologist. Thirty-eight subjects decided not to complete online questionnaires (see the  
151 section below), and thus their data could not be studied. Additionally, one participant was an  
152 outlier with more than three standard deviations lower NSS than the mean and was excluded  
153 from the analysis. The final set consisted thus of 80 participants: 39 males and 41 females  
154 with an age range from 19 to 52 years ( $M_{\text{age}} = 28.8$ ;  $SD = 7.8$ ).

### 155 **Questionnaires**

156 Noise sensitivity was assessed using the Weinstein's Noise Sensitivity Scale (Weinstein,  
157 1978). The questionnaire consists of 21 statements to rank on a 6-point Likert scale ranging  
158 from "agree strongly" to "disagree strongly". Fourteen items were reverse-scored. The total  
159 sum represents noise sensitivity score (NSS), and a higher score corresponds to higher  
160 sensitivity. The questionnaire was distributed as a part of an online Helsinki Inventory of  
161 Music and Affective Behaviors (HIMAB, Burunat et al., 2017, 2015; Gold et al., 2013; Kliuchko,  
162 2017). The inventory completion was left to participants' choice depending on how much time  
163 they were willing to dedicate to the Tunteet protocol.

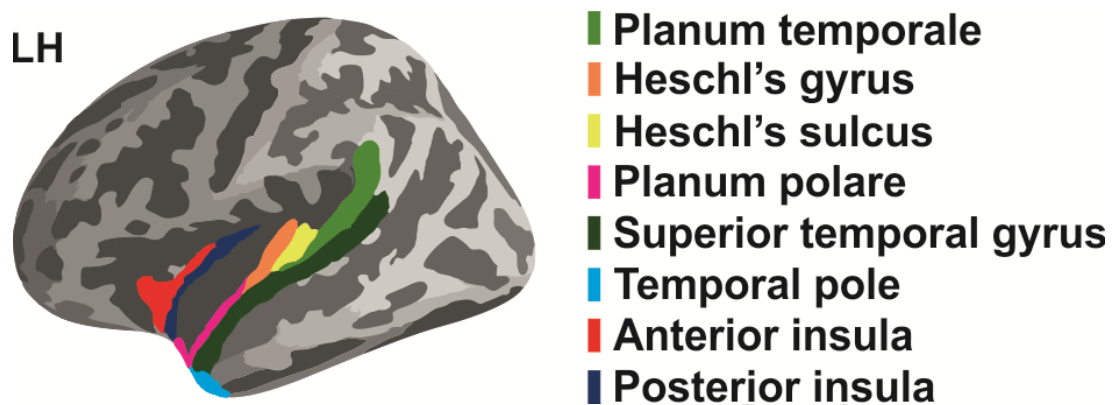
#### 164 **MRI data acquisition**

165 This study was conducted in the Advanced Magnetic Imaging (AMI) Centre at Aalto University,  
166 Espoo, Finland. A Siemens Magnetom Skyra 3 T whole-body scanner (Siemens Healthcare,  
167 Erlangen, Germany) and a standard 20-channel head-neck coil was used. Noise-attenuating  
168 headphones and foam cushions were used for hearing protection. A gradient-echo (MP-RAGE)  
169 T1-weighted sequence with repetition time, echo time, inversion time, and flip angle of 2530  
170 ms, 3.3 ms, 1100 ms, and 7 degrees, respectively, was used. Voxel size was 1 mm<sup>3</sup>.

#### 171 **MRI data processing**

172 Surface-based morphometry was performed with FreeSurfer (Dale et al., 1999; Fischl et al.,  
173 1999) using an automated procedure. Differences in cortical structure related to noise  
174 sensitivity were quantified within regions of interest (ROIs) based on sulco-gyral anatomy  
175 (Destrieux et al., 2010). For the analysis we chose primary and non-primary areas of the  
176 auditory cortex: (1) Heschl's gyrus; (2) Heschl's sulcus; (3) lateral part of superior temporal  
177 gyrus; (4) planum polare; (5) planum temporale; and (6) temporal pole. Besides from the  
178 auditory cortex, we included into the analysis the structures of the bilateral insular cortex: (7)

179 combined long insular gyrus and central sulcus of the insula (posterior insula); and (8) short  
 180 insular gyrus (anterior insula). Hippocampus and amygdala were the subcortical structures  
 181 chosen for the analysis. Cortical areas selected for the analysis are shown in Figure 1.



**Figure 1.** Lateral view of a brain showing a parcellation scheme of eight selected regions of interest (ROIs) projected onto an inflated standard brain. Bilateral structures were used even if only the left hemisphere (LH) is illustrated.

182

### 183 Statistical analysis

184 Volumes of each ROI were proportionally adjusted for the intracranial volume to control for  
 185 differences in head size. Cortical thickness of each ROI was corrected for mean cortical  
 186 thickness. We took into consideration that age is known to decrease volume, thickness,  
 187 surface area, and folding of cortical structures (Lemaitre et al., 2012; Thambisetty et al., 2010;  
 188 Toga et al., 2011). Moreover, in our data age positively, but non-significantly, correlated with  
 189 NSS ( $r = 0.207$ ,  $P = 0.066$ ). According to that, age was included in the statistical models to  
 190 assure that the observed effects are not explained by age differences.

191 To test the effect of noise sensitivity on each morphological measure, we first applied a  
 192 general linear model (GLM) with Hemisphere (two levels) and ROI (eight levels, except for GM  
 193 volume for which together with subcortical structures the number of levels was ten) as

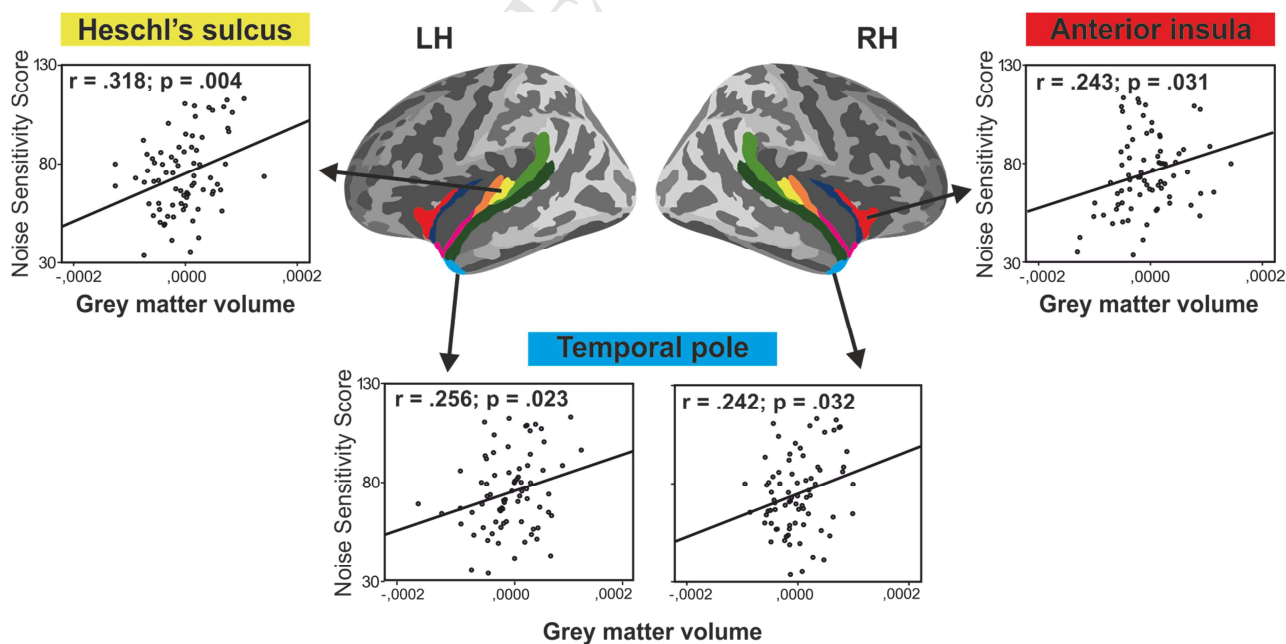
194 within-subjects factors. NSS served as a regressor of interest. Age was added to the model as  
195 an additional regressor. Within-subjects effects were Greenhouse-Geisser-corrected. After  
196 identifying in which morphological measures there was an effect of noise sensitivity, we  
197 applied two-tailed partial correlations controlling for Age to evaluate directionality and  
198 strength of the association in each ROI. False discovery rate (FDR) correction for multiple  
199 testing was applied.

## 200 **RESULTS**

201 The scores in the Weinstein's Noise Sensitivity Scale (NSS) ranged from 44 to 121 with a mean  
202 value of  $81.7 \pm 17.0$  (mean  $\pm$  SD). NSS did not differ between males and females ( $F_{1,79} = 2.83$ ,  
203  $P = 0.096$ ) and was positively but non-significantly correlated with age ( $r = 0.207$ ,  $P = 0.066$ ).

204 NSS showed a significant main effect on GM volume ( $F_{1,77} = 5.97$ ,  $P = 0.017$ ,  $\eta^2 = 0.072$ ): the  
205 larger GM volumes, the higher NSS. This effect was of an opposite direction to that of Age,  
206 which was also found significant ( $F_{1,77} = 7.07$ ,  $P = 0.010$ ,  $\eta^2 = 0.084$ ): the older age  
207 corresponded to smaller GM volumes. The main effects of ROI ( $F_{1,693} = 80.8$ ,  $P < 0.0001$ ,  $\eta^2 = 0.512$ )  
208 as well as the interaction Hemisphere by ROI ( $F_{1,693} = 3.12$ ,  $P = 0.014$ ,  $\eta^2 = 0.039$ )  
209 suggested that the structures varied in GM volume, and there were hemispheric differences  
210 depending on the area. Cortical thickness differed depending on the ROI ( $F_{1,77} = 9.02$ ,  $P <$   
211  $0.0001$ ,  $\eta^2 = 0.105$ ), which, in turn, was differently affected by Age depending on the cortical  
212 structure (ROI  $\times$  Age:  $F_{1,77} = 3.79$ ,  $P = 0.002$ ,  $\eta^2 = 0.047$ ). There was no overall effect of NSS  
213 on the cortical thickness ( $P = 0.095$ ). The analysis of cortical folding ( $F_{1,77} = 3.36$ ,  $P = 0.071$ ,  
214  $\eta^2 = 0.042$ ) and cortical area ( $F_{1,77} = 1.49$ ,  $P = 0.226$ ,  $\eta^2 = 0.019$ ) did not show significant  
215 main effects and interactions of NSS with these measures.

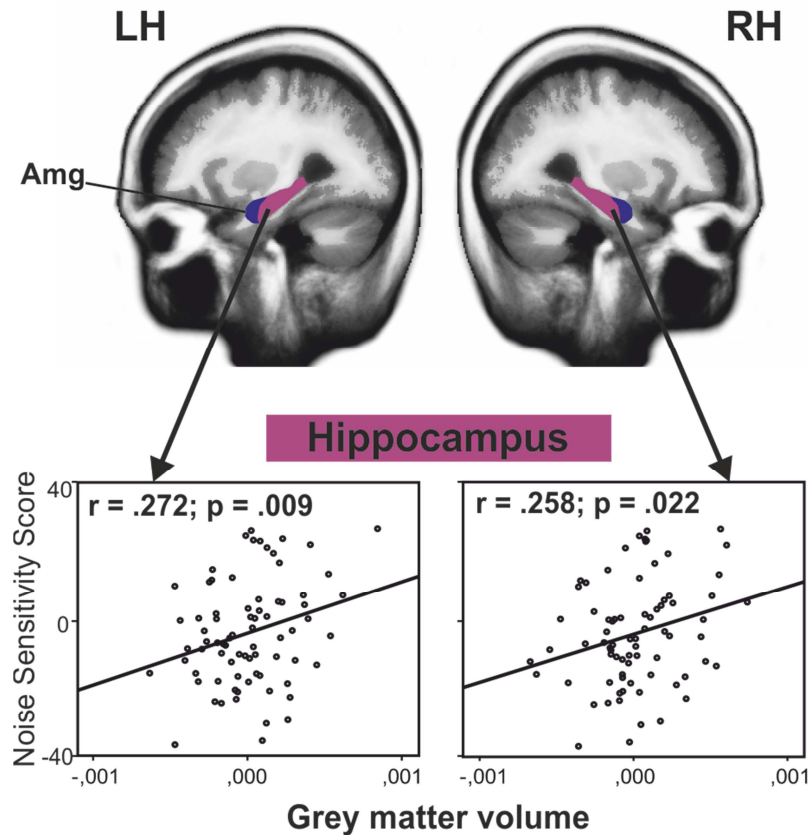
216 Thus, the analysis revealed that GM volume, but not cortical thickness, folding or area, was  
 217 significantly affected by noise sensitivity. Hence, we focused our further analysis on  
 218 investigating the relationship between NSS and cortical anatomy in each of the ROI using GM  
 219 volume measures only. For that, we applied partial correlations controlling for the effects of  
 220 Age. We note that none of the performed correlations survived the correction, and we further  
 221 report observation based on uncorrected P-values. FDR-adjusted P-values as well as the  
 222 correlation coefficients obtained in all ROIs are reported in Inline Supplementary Table 1.  
 223 Based on the findings, uncorrected for multiple comparisons, we observed an association  
 224 between NSS and GM volume in the left and right temporal poles ( $r = 0.256$ ,  $P_{\text{uncorr}} = 0.023$ ,  
 225 and  $r = 0.242$ ,  $P_{\text{uncorr}} = 0.032$ , respectively), left Heschl's sulcus ( $r = 0.318$ ,  $P_{\text{uncorr}} = 0.004$ ), right  
 226 anterior insula ( $r = 0.243$ ,  $P_{\text{uncorr}} = 0.031$ ), as well as the left and right hippocampi ( $r = 0.272$ ,  
 227  $P_{\text{uncorr}} = 0.015$ , and  $r = 0.258$ ,  $P_{\text{uncorr}} = 0.022$ , respectively). In all structures, a larger GM  
 228 corresponded to a larger NSS. Figure 1 illustrates the correlations observed in the cortical  
 229 structures, whereas Figure 2 shows the correlation of NSS with hippocampal GM volume.



**Figure 2.** Noise sensitivity-related changes in the grey matter volume of cortical structures. Grey matter volume is corrected for the intracranial volume and age. Noise sensitivity score is

corrected for age. *P-values are uncorrected*. LH – left hemisphere; RH – right hemisphere.

230



**Figure 3.** Noise sensitivity-related changes in the grey matter volume of the hippocampus. Grey matter volume is corrected for subjects' age and the intracranial volume. Noise sensitivity score is corrected for age. *P-values are uncorrected*. LH – left hemisphere; RH – right hemisphere; Amg – amygdala.

231

## 232 Discussion

233 This study aimed to explore morphological markers associated with noise sensitivity. We  
 234 focused our research on the brain areas involved with auditory processing, attributing  
 235 emotions to sounds, detecting their salience and regulating bodily functions in response to  
 236 auditory events. Our data suggest that noise sensitivity is related to changes in GM volume

237 over the selected areas. In particular, we propose that higher noise sensitivity may be related  
238 to enlarged GM volumes in the bilateral temporal pole, the left Heschl's sulcus, the right  
239 anterior insula, and bilateral hippocampus. However, we point out that the observed  
240 associations did not survive a correction for multiple comparisons and are only suggested as  
241 candidate areas for an involvement with noise sensitivity. The potential roles of the left  
242 Heschl's sulcus, the right anterior insula, as well as the bilateral hippocampus and temporal  
243 pole in noise sensitivity are further discussed.

244 We expected to observe noise sensitivity-related changes to the volume of the auditory cortex  
245 structures and found a trend of an increase of the left-hemispheric Heschl's sulcus volume  
246 with higher noise sensitivity. The Heschl's sulcus is adjacent to Heschl's gyrus, which contains  
247 the primary auditory cortex (Abdul-Kareem and Sluming, 2008). Pre-existent as well as  
248 training-induced differences in the morphology of Heschl's gyrus are shown to relate to its  
249 function (Schneider et al., 2002; Warrier et al., 2009). We can assume that the volumetric  
250 differences that we observed in this area have a relationship to an altered auditory processing  
251 in noise sensitivity. Accordingly, diminished abilities for sensory gating and discrimination of  
252 sound noisiness in noise-sensitive individuals were demonstrated in recent  
253 electrophysiological studies (Kliuchko et al., 2016; Shepherd et al., 2016). Remarkably, we  
254 found that the volume of Heschl's sulcus was related to noise sensitivity only in the left  
255 hemisphere. The function of the primary auditory cortex is functionally separated in terms of  
256 its involvement with spectro-temporal processing where the right hemisphere mostly  
257 attributed with spectral processing and the left hemisphere with temporal processing  
258 (Zatorre et al., 2002). It is also proposed that the functional asymmetry of the auditory cortex  
259 is related to asymmetry in temporal sampling (Poeppl, 2003). According to this view, the left  
260 hemisphere is recruited in processing rapid acoustic changes in temporal integration

261 windows of tens of milliseconds, whereas the right hemisphere is preferentially involved with  
262 processing slow changes over the time span of hundreds of milliseconds. The enlarged volume  
263 of the left core auditory cortex area could indicate that the central sound processing in noise  
264 sensitivity is altered in analysing the fine temporal aspects of auditory information (Warrier  
265 et al., 2009). These findings call for further investigation of the functional organization of  
266 auditory processing in noise-sensitive individuals.

267 The temporal pole was another structure that we found to be potentially associated with  
268 noise sensitivity in both hemispheres. The temporal pole is an anterior-most part of the  
269 temporal lobe. It is thought to belong to the paralimbic brain and is attributed with multiple  
270 cognitive functions, one of which is an integration of higher-order processed stimuli and  
271 perceived events with emotions (Olson et al., 2007). Functional studies have indicated the  
272 temporal pole to be involved in emotion, especially with self-induced states of sadness,  
273 anxiety, and happiness (Kimbrell et al., 1999; Pelletier et al., 2003). The temporal pole is  
274 connected within secondary and associative auditory areas in the temporal lobe. Moreover, it  
275 is highly interconnected with the amygdala and receives inputs from the insular cortex (Olson  
276 et al., 2007; Pascual et al., 2015). Notably, the temporal pole is functionally connected with the  
277 hippocampus (Pascual et al., 2015), which, too, showed a bilateral positive association of its  
278 GM volume and noise sensitivity in our study. Besides the auditory system, the temporal pole  
279 receives input from visual and olfactory systems and serves as a structure of sensory-  
280 emotional coupling for these modalities as well (Olson et al., 2007). The activation of the  
281 temporal pole induced by auditory, visual, or olfactory information seems to follow a  
282 dorsal/ventral segregation with auditory stimuli activating its dorsal part (Olson et al., 2007).  
283 However, the parcellation approach used in our study did not allow us to determine more  
284 precisely which part of the temporal pole was specifically enlarged. Some studies report that



285 noise sensitivity overlaps with other environmental sensitivities, such as odour intolerance,  
286 and it is debated whether they are concomitant or independent (Shepherd et al., 2015).  
287 Further investigation of the structure of the temporal pole and its functional involvement with  
288 sensory intolerances could be beneficial for understanding whether environmental  
289 sensitivities are specific to a single sensory domain.

290 Noise sensitivity was positively associated with the volume of the left and right hippocampus.  
291 The primary role of the hippocampus is related to memory and learning; however, it has been  
292 reported to participate in the processing of the emotional content of music (Mitterschiffthaler  
293 et al., 2007) and identification of stimulus novelty (Lieberman et al., 2009; Thoma et al., 2008)  
294 as well. The hippocampus together with amygdala is important for aversive learning.  
295 However, their roles in this process are differential: the amygdala plays a role in detecting  
296 salience of a stimulus (Zheng et al., 2017) and determines an autonomic response to it  
297 (Cacciaglia et al., 2014), whereas the hippocampus is involved with memory and contextual  
298 processing (Phelps, 2004). Hippocampal volume is related to awareness of the relation  
299 between a conditional and an unconditional stimulus and thus demonstrates that the relative  
300 volume of the bilateral hippocampus in healthy people moderates aversive learning  
301 (Cacciaglia et al., 2014). Considering the observed relationship between volumes of the left  
302 and right hippocampus and noise sensitivity score, we may speculate that noise sensitivity is  
303 related to the ability to form the associations between negative emotional experience and  
304 noise.

305 We predicted that noise sensitivity could be related to the morphology of the insular cortex.  
306 Indeed, we observed a potential positive association between the anterior insula in the right  
307 hemisphere and noise sensitivity. Previous structural, functional and electrophysiological  
308 studies linked the right insula to distress caused by tinnitus (Golm et al., 2016; Leaver et al.,

309 2012; Van Der Loo et al., 2011; Vanneste et al., 2010). Also, an increase in insular activity was  
310 observed when subjects with tinnitus were asked to try to diminish their tinnitus (Haller et  
311 al., 2010). Kumar et al. (2017) identified anterior insula as a key region that separates  
312 misophonics and healthy controls during perception of misophonia-triggering sounds.  
313 Moreover, the study found a stronger connectivity of the anterior insula with structures  
314 regulating emotions, including hippocampus and amygdala, and its modulating role on skin  
315 conductance and heart rate responses to triggering sounds (Kumar et al., 2017).

316 The increase in volume of the anterior insula, which we observed, is probably related to the  
317 interoceptive processing (Craig, 2009). When the awareness of one's bodily state is  
318 continuously increased, whether involuntary (e.g. feeling pain) or voluntary (e.g. controlling  
319 breath), neuroplastic changes can be identified in this region. For instance, the right anterior  
320 insula progressively thickens with years of suffering from irritable bowel syndrome  
321 (Blankstein et al., 2010). A thicker right anterior insula is also found in meditation  
322 practitioners who have been learning to concentrate on interoceptive stimuli from their body,  
323 such as breathing, for many years (Lazar et al., 2005). Musical practice can enhance the  
324 behavioural accuracy of interoception: musicians are better at discriminating their heartbeat  
325 than non-musicians (Schirmer-Mokwa et al., 2015). Moreover, the increased heartbeat  
326 perception accuracy is accounted for by the length of musical training in singers (Schirmer-  
327 Mokwa et al., 2015), for whom the right anterior insula is an important node for sensory  
328 integration and salience evaluation during vocal production (Kleber et al., 2017, 2013). The  
329 explicit awareness of internal bodily state appears to be exclusively tied to the function of the  
330 right anterior insula (Critchley et al., 2004). Interoception is crucial for emotion appraisal  
331 (Dunn et al., 2010), and bodily responses play an important role for subjective feelings  
332 (Damasio, 2004). Individuals who are more aware of their bodily states report more intense

333 emotional experiences than less aware individuals (Barrett et al., 2004; Pollatos et al., 2007).  
334 Hence, based on the observation of a larger volume of the right anterior insula in association  
335 with noise sensitivity, we may speculate that noise-sensitive individuals might have an  
336 increased awareness of their inner state and as a consequence might react stronger to the  
337 stress effects caused by noise. This would lead them to exhibit more negative attitudes  
338 towards noise than resistant individuals do. However, these anatomy-based speculations  
339 should be followed up by studies on bodily awareness in noise-sensitive individuals.

340 The amygdala could be one of the structures that are associated with noise sensitivity based  
341 on its role in evaluating emotions from sensory stimuli and rich connections to the auditory  
342 system. However, the results did not reveal an association between amygdala's volume and  
343 noise sensitivity. Despite the lack of the structural differences found, it remains an open  
344 question whether noise sensitivity is related to the amygdalar function. An fMRI study of  
345 tinnitus revealed that the amygdala was activated in response to pleasant and unpleasant  
346 emotional stimuli only in healthy controls but not in tinnitus patients (Carpenter-Thompson  
347 et al., 2014). Instead, in subjects with tinnitus, the insula and parahippocampus were largely  
348 activated during the presentation of negative emotional stimuli (Carpenter-Thompson et al.,  
349 2014). Perhaps, similarly to tinnitus patients, noise-sensitive persons employ an alternative  
350 strategy for affective processing. Moreover, in an fMRI study of emotion perception in sensory  
351 processing sensitivity (SPS; Aron et al. 2011), which is a trait determining high  
352 responsiveness to environmental and social stimuli, the amygdala's activation did not  
353 differentiate highly sensitive persons from non-sensitive ones (Acevedo et al., 2014).  
354 However, the activation of the insula in response to emotional stimuli increased as a function  
355 of SPS. Based on these observations, Acevedo et al. (2014) suggested that SPS is not related to  
356 attributing emotion to sensory stimuli, but to a greater sensitivity to inner and outer

357 environments in general. An increased volume of the right anterior insula and invariant  
358 volume of the amygdala in relation to NSS in our study may be an indication for a similar role  
359 of insula vs. amygdala in noise sensitivity. Future research should aim for testing this  
360 assumption with functional neuroimaging measures.

361 We are tempted to conclude that the differences in the brain morphology related to noise  
362 sensitivity are use-dependent. However, we cannot rule out a potential contribution of genetic  
363 factors. Perhaps, noise-sensitive individuals are born with a predisposition for larger volumes  
364 of the primary auditory cortex, anterior insula, and hippocampus, leading them to be more  
365 prone to evaluate aversively environmental (auditory) stimuli. Noise sensitivity has  
366 previously been shown to aggregate in families, and twin analyses provided an estimate of  
367 heritability of 36% (Heinonen-Guzejev et al., 2005). Moreover, in a rare genetic disorder  
368 called Williams syndrome, in which noise sensitivity is often comorbid, there is a structural  
369 and functional augmentation of the left auditory cortex that cannot be explained by training  
370 but by genetics (Wengenroth et al., 2010). Hence, at least in a clinical population, it is possible  
371 that structural brain differences are pre-existent. Whether this could be the case for noise-  
372 sensitive but healthy individuals is a question requiring further investigation.

373 Taken together, in our exploratory study we propose that based on the observation of a  
374 change in the GM volume, several brain structures should be investigated further for their role  
375 in noise sensitivity. Namely, we suggest that enlargements in the left Heschl's sulcus, bilateral  
376 temporal pole, right anterior insula as well as bilateral hippocampus could be related to high  
377 noise sensitivity. We call for confirmatory investigations. Another interesting direction for  
378 future research is to address whether anatomical and functional connections between these  
379 brain areas are affected in noise sensitivity.

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