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Title: Neuroanatomical substrate of noise sensitivity

Year: 2018

Version:

Please cite the original version:

Kliuchko, M., Puoliväli, T., Heinonen-Guzejev, M., Tervaniemi, M., Toiviainen, P., Sams, M., & Brattico, E. (2018). Neuroanatomical substrate of noise sensitivity. NeuroImage, 167, 309-315. https://doi.org/10.1016/j.neuroimage.2017.11.041

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Accepted Manuscript

Neuroanatomical substrate of noise sensitivity

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PII: S1053-8119(17)30973-4

DOI: 10.1016/j.neuroimage.2017.11.041

Reference: YNIMG 14488

To appear in: NeuroImage

Received Date: 4 April 2017

Accepted Date: 20 November 2017

Please cite this article as: Kliuchko, M., Puoliväli, T., Heinonen-Guzejev, M., Tervaniemi, M., Toiviainen, P., Sams, M., Brattico, E., Neuroanatomical substrate of noise sensitivity, *NeuroImage* (2017), doi: 10.1016/j.neuroimage.2017.11.041.

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1 Neuroanatomical substrate of noise sensitivity

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22 Abstract

Recent functional studies suggest that noise sensitivity, a trait describing attitudes towards 23 24 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 25 26 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 27 28 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. 29 30 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 31 32 to auditory perceptual, emotional and interoceptive processing, in which larger grey matter volume seems to be related to higher noise sensitivity. 33

34

35 Keywords

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

37 Introduction

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

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

discomfort (Persson et al., 2007; Weinstein, 1978). In the present study, we aimed at 61 investigating whether morphological variations in the structure of auditory and non-auditory 62 brain areas dedicated to sensory-emotional processing and evaluation of auditory 63 information could be related to noise sensitivity. 64 Recent electrophysiological studies have associated noise sensitivity with neural deficits in 65 central auditory function, advocating for a perceptual/sensory component to noise sensitivity. 66 As such, highly noise-sensitive individuals were found to exhibit altered sensory gating 67 (Shepherd et al., 2016) and pre-attentive discrimination of sound noisiness (Kliuchko et al., 68 69 2016). These functional changes could be paralleled by anatomical differences in the central auditory structures. The relation between function and structure of auditory areas is found, 70 71 for instance, in autistic patients. They are reported to have reduced volume of the planum temporale (Rojas et al., 2002), which is involved with segregation and matching 72 spectrotemporal auditory information (Griffiths and Warren, 2002). Poor abilities in 73 segregating relevant acoustic signals, in turn, are related to the sound intolerance that is 74

exhibited in autistic patients (Lodhia et al., 2014). If noise sensitivity is related to deficits in
the auditory processing, we could expect a negative relationship between noise sensitivity
and the size of auditory cortical areas. On the other hand, their enlargement could mean an
involvement of wider areas into sound processing that could result in hypersensitivity to
sounds.

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

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

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

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

In addition to the auditory cortex, amygdala, and hippocampus, an important role in stimulus 112 evaluation is played by insula. A recent study found that the insula is related to symptoms of a 113 distress caused by tinnitus but not to the characteristics of tinnitus itself, such as its loudness 114 (Leaver et al., 2012). Further, in misophonia (an affective disorder characterized by negative 115 emotions towards specific sounds, such as chewing or swallowing) the activation of bilateral 116 anterior insula increased parallelly with higher subjective misophonic distress caused by a 117 triggering sound (Kumar et al., 2017). Other studies propose that anterior insula is involved in 118 anticipation of aversive bodily states and negative emotions (Phelps et al., 2001). Moreover, 119 insula, along with the amygdala and the hippocampus, can have an influence on autonomic 120 functions. Shepherd and colleagues (2016) observed differences in the dynamics of heart rate 121 in response to emotional stimuli and heart rate variability between noise-sensitive and noise-122 resistant groups. Changes in heart rate serve as indices of noise sensitivity affecting 123 integration between central and autonomic nervous systems (Thayer and Lane, 2000). Hence, 124 we expected that noise sensitivity could be related to the structure of the insular cortex that is 125 involved in regulating autonomic functions and plays a major role in the interoceptive feeling. 126 As the insular cortex and, specifically, its anterior part was found enlarged in relation to 127 distress caused by sound sensitivities, such as tinnitus and misophonia (Leaver et al., 2012), 128 we could expect the same pattern of structural change to occur in relation to noise sensitivity. 129 In this study, we measured grey matter volume and morphology (cortical area, cortical 130

thickness and cortical folding) in selected regions of interest from both cerebral hemispheres,

namely auditory regions, hippocampus, amygdala, and insula, using FreeSurfer package for an

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

136 **METHODS**

137 Participants

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

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

155 Questionnaires

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

164 MRI data acquisition

This study was conducted in the Advanced Magnetic Imaging (AMI) Centre at Aalto University,
Espoo, Finland. A Siemens Magnetom Skyra 3 T whole-body scanner (Siemens Healthcare,
Erlangen, Germany) and a standard 20-channel head-neck coil was used. Noise-attenuating
headphones and foam cushions were used for hearing protection. A gradient-echo (MP-RAGE)
T1-weighted sequence with repetition time, echo time, inversion time, and flip angle of 2530
ms, 3.3 ms, 1100 ms, and 7 degrees, respectively, was used. Voxel size was 1 mm³.

171 MRI data processing

Surface-based morphometry was performed with FreeSurfer (Dale et al., 1999; Fischl et al., 1999) using an automated procedure. Differences in cortical structure related to noise sensitivity were quantified within regions of interest (ROIs) based on sulco-gyral anatomy (Destrieux et al., 2010). For the analysis we chose primary and non-primary areas of the auditory cortex: (1) Heschl's gyrus; (2) Heschl's sulcus; (3) lateral part of superior temporal gyrus; (4) planum polare; (5) planum temporale; and (6) temporal pole. Besides from the 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
- 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,
- 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
- NSS (r = 0.207, P = 0.066). According to that, age was included in the statistical models to
- 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
- volume for which together with subcortical structures the number of levels was ten) as

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

200 RESULTS

The scores in the Weinstein's Noise Sensitivity Scale (NSS) ranged from 44 to 121 with a mean value of 81.7 ± 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).

NSS showed a significant main effect on GM volume (F1,77 = 5.97, P = 0.017, $\eta p 2 = 0.072$): the 204 larger GM volumes, the higher NSS. This effect was of an opposite direction to that of Age, 205 which was also found significant (F1,77 = 7.07, P = 0.010, $\eta p = 0.084$): the older age 206 corresponded to smaller GM volumes. The main effects of ROI (*F*1,693 = 80.8, *P* < 0.0001, np2 207 = 0.512) as well as the interaction Hemisphere by ROI (*F*1,693 = 3.12, *P* = 0.014, η p2 = 0.039) 208 209 suggested that the structures varied in GM volume, and there were hemispheric differences depending on the area. Cortical thickness differed depending on the ROI (F1,77 = 9.02, P < 100, P <210 0.0001, $\eta p2 = 0.105$), which, in turn, was differently affected by Age depending on the cortical 211 structure (ROI x Age: F1,77 = 3.79, P = 0.002, $\eta p 2 = 0.047$). There was no overall effect of NSS 212 on the cortical thickness (P = 0.095). The analysis of cortical folding (F1,77 = 3.36, P = 0.071, 213 $\eta p2 = 0.042$) and cortical area (F1,77 = 1.49, P = 0.226, $\eta p2 = 0.019$) did not show significant 214 215 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 significantly affected by noise sensitivity. Hence, we focused our further analysis on 217 investigating the relationship between NSS and cortical anatomy in each of the ROI using GM 218 volume measures only. For that, we applied partial correlations controlling for the effects of 219 Age. We note that none of the performed correlations survived the correction, and we further 220 report observation based on uncorrected P-values. FDR-adjusted P-values as well as the 221 correlation coefficients obtained in all ROIs are reported in Inline Supplementary Table 1. 222 Based on the findings, uncorrected for multiple comparisons, we observed an association 223 between NSS and GM volume in the left and right temporal poles (r = 0.256, $P_{uncorr} = 0.023$, 224 and r = 0.242, $P_{uncorr} = 0.032$, respectively), left Heschl's sulcus (r = 0.318, $P_{uncorr} = 0.004$), right 225 anterior insula (r = 0.243, $P_{uncorr} = 0.031$), as well as the left and right hippocampi (r = 0.272, 226 $P_{uncorr} = 0.015$, and r = 0.258, $P_{uncorr} = 0.022$, respectively). In all structures, a larger GM 227 corresponded to a larger NSS. Figure 1 illustrates the correlations observed in the cortical 228 structures, whereas Figure 2 shows the correlation of NSS with hippocampal GM volume. 229



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.



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**

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

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

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

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

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

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

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

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

2012; Van Der Loo et al., 2011; Vanneste et al., 2010). Also, an increase in insular activity was
observed when subjects with tinnitus were asked to try to diminish their tinnitus (Haller et
al., 2010). Kumar et al. (2017) identified anterior insula as a key region that separates
misophonics and healthy controls during perception of misophonia-triggering sounds.
Moreover, the study found a stronger connectivity of the anterior insula with structures
regulating emotions, including hippocampus and amygdala, and its modulating role on skin
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 interoceptive processing (Craig, 2009). When the awareness of one's bodily state is 317 continuously increased, whether involuntary (e.g. feeling pain) or voluntary (e.g. controlling 318 breath), neuroplastic changes can be identified in this region. For instance, the right anterior 319 insula progressively thickens with years of suffering from irritable bowel syndrome 320 (Blankstein et al., 2010). A thicker right anterior insula is also found in meditation 321 practitioners who have been learning to concentrate on interoceptive stimuli from their body, 322 such as breathing, for many years (Lazar et al., 2005). Musical practice can enhance the 323 behavioural accuracy of interoception: musicians are better at discriminating their heartbeat 324 than non-musicians (Schirmer-Mokwa et al., 2015). Moreover, the increased heartbeat 325 perception accuracy is accounted for by the length of musical training in singers (Schirmer-326 Mokwa et al., 2015), for whom the right anterior insula is an important node for sensory 327 integration and salience evaluation during vocal production (Kleber et al., 2017, 2013). The 328 explicit awareness of internal bodily state appears to be exclusively tied to the function of the 329 right anterior insula (Critchley et al., 2004). Interoception is crucial for emotion appraisal 330 (Dunn et al., 2010), and bodily responses play an important role for subjective feelings 331 (Damasio, 2004). Individuals who are more aware of their bodily states report more intense 332

emotional experiences than less aware individuals (Barrett et al., 2004; Pollatos et al., 2007).
Hence, based on the observation of a larger volume of the right anterior insula in association
with noise sensitivity, we may speculate that noise-sensitive individuals might have an
increased awareness of their inner state and as a consequence might react stronger to the
stress effects caused by noise. This would lead them to exhibit more negative attitudes
towards noise than resistant individuals do. However, these anatomy-based speculations
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 on its role in evaluating emotions from sensory stimuli and rich connections to the auditory 341 system. However, the results did not reveal an association between amygdala's volume and 342 noise sensitivity. Despite the lack of the structural differences found, it remains an open 343 question whether noise sensitivity is related to the amygdalar function. An fMRI study of 344 tinnitus revealed that the amygdala was activated in response to pleasant and unpleasant 345 346 emotional stimuli only in healthy controls but not in tinnitus patients (Carpenter-Thompson et al., 2014). Instead, in subjects with tinnitus, the insula and parahippocampus were largely 347 activated during the presentation of negative emotional stimuli (Carpenter-Thompson et al., 348 2014). Perhaps, similarly to tinnitus patients, noise-sensitive persons employ an alternative 349 strategy for affective processing. Moreover, in an fMRI study of emotion perception in sensory 350 processing sensitivity (SPS; Aron et al. 2011), which is a trait determining high 351 responsiveness to environmental and social stimuli, the amygdala's activation did not 352 differentiate highly sensitive persons from non-sensitive ones (Acevedo et al., 2014). 353 However, the activation of the insula in response to emotional stimuli increased as a function 354 of SPS. Based on these observations, Acevedo et al. (2014) suggested that SPS is not related to 355 attributing emotion to sensory stimuli, but to a greater sensitivity to inner and outer 356

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

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

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

380 Acknowledgments

- 381 The work was financially supported by the Academy of Finland (project numbers 272250,
- 274037). The first author of this paper received support from the Doctoral programme for
- 383 Psychology, learning and communication, University of Helsinki. Center for Music in the Brain
- is funded by the Danish National Research Foundation (DNRF117). We wish to thank Dr.
- 385 Brigitte Bogert, Benjamin Gold and Marita Kattelus for conducting the MRI measurements,
- and Vittoria Spinosa for assistance with scoring. We thank Laura Hedlund and Hella Kastbjerg
- 387 for proofreading. We also thank the neuroradiologist Jussi Numminen for evaluating the
- 388 anatomical images of the subjects.

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