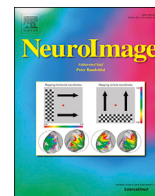




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Neuroanatomical substrate of noise sensitivity

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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.

Introduction

Noise, described as an any unwanted sound irrespective to its physical properties, can 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., 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 environmental noise is *noise sensitivity*. Noise sensitivity describes a stable individual trait that determines a general attitude towards noise ([Stansfeld, 1992](#)). According to the definition of [Job \(1999\)](#), it refers to physiological and psychological (also including attitudinal) internal states of any individual, which determines reactivity to noise. Noise sensitivity predicts noise annoyance ([Stansfeld, 1992](#); [van Kamp et al., 2004](#)), and it influences one's evaluation of the soundscape's pleasantness ([Lindborg and Friberg, 2016](#)). Moreover, noise sensitivity moderates one's daily behaviour; for instance, noise-sensitive individuals

rarely have music in the background ([Kliuchko et al., 2015](#)) and often use hearing protection at work ([Heinonen-Guzejev et al., 2011](#)).

Noise sensitivity has not been linked to the acuity of peripheral hearing, intensity discrimination, or auditory reaction time ([Ellermeier et al., 2001](#); [Heinonen-Guzejev et al., 2011](#); [Stansfeld et al., 1985](#)). However, it is shown to be related to the mechanisms of the central sound processing ([Kliuchko et al., 2016](#); [Shepherd et al., 2016](#)). Noise sensitivity is also correlated with annoyance induced by noise ([Heinonen-Guzejev, 2008](#)), which suggests that noise-sensitive individuals develop affective reaction towards noise easier than noise-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 and self ([Watson and Clarck, 1984](#)) as well as exhibiting increased responses to stress and discomfort ([Persson et al., 2007](#); [Weinstein, 1978](#)). In the present study, we aimed at investigating whether morphological variations in the structure of auditory and non-auditory brain areas dedicated to sensory-emotional processing

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and evaluation of auditory information could be related to noise sensitivity.

Recent electrophysiological studies have associated noise sensitivity with neural deficits in central auditory function, advocating for a perceptual/sensory component to noise sensitivity. As such, highly noise-sensitive individuals were found to exhibit altered sensory gating (Shepherd et al., 2016) and pre-attentive discrimination of sound noisiness (Kliuchko et al., 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, 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 spectrottemporal auditory information (Griffiths and Warren, 2002). Poor abilities in segregating relevant acoustic signals, in turn, are related to the sound intolerance that is 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 stimulation, and this activation is coupled with anxiety-like behaviours (Herry et al., 2007). The hippocampus is also involved on auditory information processing and contributes to sensory gating, which is an inhibition of irrelevant, repetitive sensory input (Cromwell et al., 2008). Moreover, the amygdala-hippocampal complex displays a unidirectional coupling during processing of emotionally important stimuli, so that amygdala detects a stimulus' salience and then influences dynamics of the hippocampal response to it (Zheng et al., 2017). In turn, hippocampus-dependent memory representations of stimulus emotional significance can influence amygdala function (Phelps, 2004).

Both the hippocampus and amygdala have rich connections with auditory areas of the brain. 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 potentially influence the processing of an auditory stimulus even before it reaches the cortex (Marsh et al., 2002). The hippocampus, in turn, does not have direct connections with the primary and secondary auditory cortical areas (Mohedano-Moriano et al., 2007), but it is largely interconnected with auditory associative areas either directly or via pathways coming 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 loss) with the neuroplastic changes in its functional and structural organization (Kraus and Canlon, 2012). Moreover, the volume of amygdala and hippocampus is known to decrease in chronic stress (Abdalla and Geha, 2017), and small hippocampus is predictive for pathological stress responses (Gilbertson et al., 2002). In relation to noise sensitivity, an increase and decrease in amygdala and hippocampal volumes could be expected alike. A larger volume of these structures could indicate increased activation of amygdala during sound processing, 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 evaluation is played by insula. A recent study found that the insula is related to symptoms of a distress caused by tinnitus but not to the characteristics of tinnitus itself, such as its loudness (Leaver et al., 2012). Further, in misophonia (an affective disorder

characterized by negative emotions towards specific sounds, such as chewing or swallowing) the activation of bilateral anterior insula increased parallelly with higher subjective misophonic distress caused by a triggering sound (Kumar et al., 2017). Other studies propose that anterior insula is involved in anticipation of aversive bodily states and negative emotions (Phelps et al., 2001). Moreover, insula, along with the amygdala and the hippocampus, can have an influence on autonomic functions. Shepherd et al. (2016) observed differences in the dynamics of heart rate in response to emotional stimuli and heart rate variability between noise-sensitive and noise-resistant groups. Changes in heart rate serve as indices of noise sensitivity affecting integration between central and autonomic nervous systems (Thayer and Lane, 2000). Hence, we expected that noise sensitivity could be related to the structure of the insular cortex that is involved in regulating autonomic functions and plays a major role in the interoceptive feeling. As the insular cortex and, specifically, its anterior part was found enlarged in relation to distress caused by sound sensitivities, such as tinnitus and misophonia (Leaver et al., 2012), we could expect the same pattern of structural change to occur in relation to noise sensitivity.

In this study, we measured grey matter volume and morphology (cortical area, cortical 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.

Methods

Participants

The experimental procedure for this study was included in the research protocol “Tunteet” (Emotions), which was approved by the Coordinating Ethics Committee of the Hospital 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 University of Helsinki. The inclusion criteria consisted of MRI safety considerations as well as the absence of hearing, neurological and psychiatric problems. All participants gave their written consent to participate in the study prior to the experiment. They were compensated for their time spent in the laboratory, traveling and filling questionnaires online by culture vouchers.

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

Questionnaires

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

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°, respectively, was used. Voxel size was 1 mm³.

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

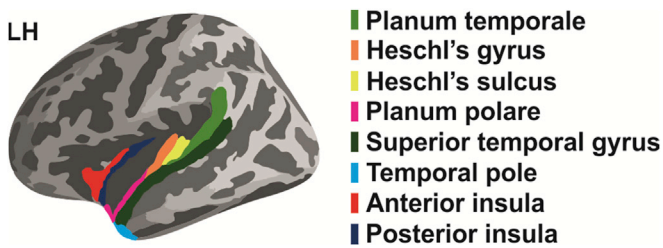


Fig. 1. Lateral view of a brain showing a parcellation scheme of eight selected regions of interest (ROIs) projected onto an inflated standard brain. Bilateral structures were used even if only the left hemisphere (LH) is illustrated.

Statistical analysis

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 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; 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.

To test the effect of noise sensitivity on each morphological measure, we first applied a 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.

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 ($F_{1,79} = 2.83$, $P = 0.096$) and was positively but non-significantly correlated with age ($r = 0.207$, $P = 0.066$).

NSS showed a significant main effect on GM volume ($F_{1,77} = 5.97$, $P = 0.017$, $\eta^2 = 0.072$): the larger GM volumes, the higher NSS. This effect was of an opposite direction to that of Age, which was also found significant ($F_{1,77} = 7.07$, $P = 0.010$, $\eta^2 = 0.084$): the older age corresponded to smaller GM volumes. The main effects of ROI ($F_{1,693} = 80.8$, $P < 0.0001$, $\eta^2 = 0.512$) as well as the interaction Hemisphere by ROI ($F_{1,693} = 3.12$, $P = 0.014$, $\eta^2 = 0.039$) suggested that the structures varied in GM volume, and there were hemispheric differences depending on the area. Cortical thickness differed depending

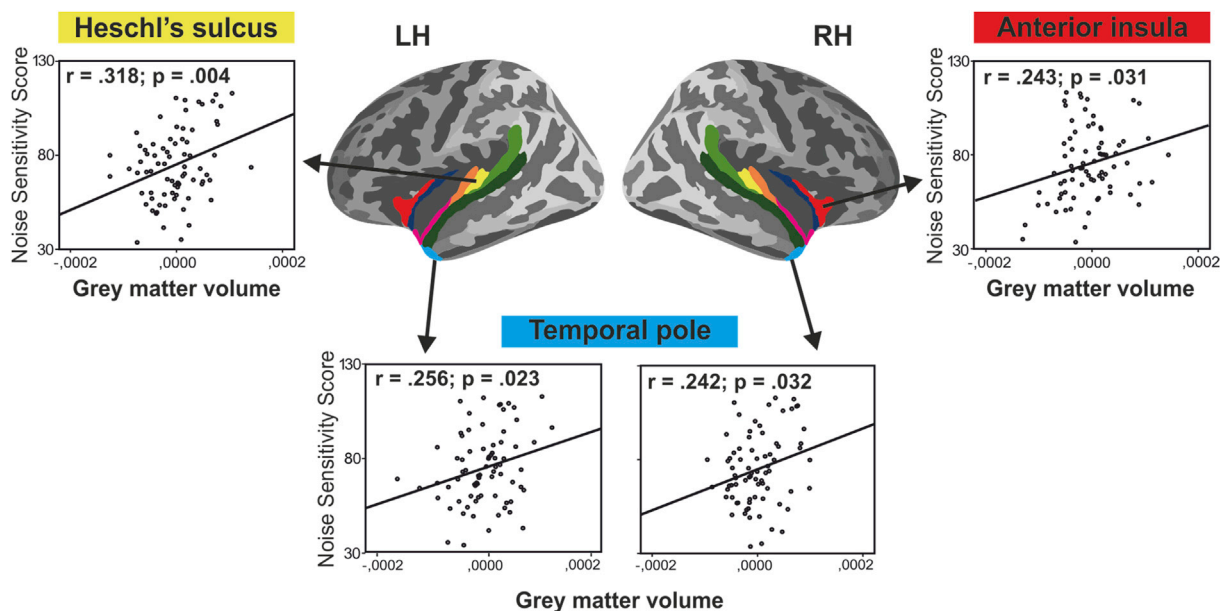


Fig. 2. Noise sensitivity-related changes in the grey matter volume of cortical structures. Grey matter volume is corrected for the intracranial volume and age. Noise sensitivity score is corrected for age. P-values are uncorrected. LH – left hemisphere; RH – right hemisphere.

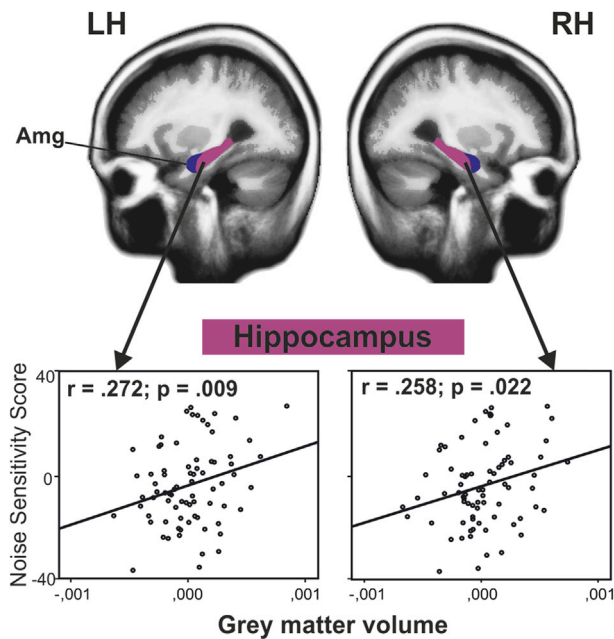


Fig. 3. Noise sensitivity-related changes in the grey matter volume of the hippocampus. Grey matter volume is corrected for subjects' age and the intracranial volume. Noise sensitivity score is corrected for age. P-values are uncorrected. LH – left hemisphere; RH – right hemisphere; Amg – amygdala.

on the ROI ($F_{1,77} = 9.02$, $P < 0.0001$, $\eta^2 = 0.105$), which, in turn, was differently affected by Age depending on the cortical structure (ROI x Age: $F_{1,77} = 3.79$, $P = 0.002$, $\eta^2 = 0.047$). There was no overall effect of NSS on the cortical thickness ($P = 0.095$). The analysis of cortical folding ($F_{1,77} = 3.36$, $P = 0.071$, $\eta^2 = 0.042$) and cortical area ($F_{1,77} = 1.49$, $P = 0.226$, $\eta^2 = 0.019$) did not show significant main effects and interactions of NSS with these measures.

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 investigating the relationship between NSS and cortical anatomy in each of the ROI using GM volume measures only. For that, we applied partial correlations controlling for the effects of Age. We note that none of the performed correlations survived the correction, and we further report observation based on uncorrected P-values. FDR-adjusted P-values as well as the correlation coefficients obtained in all ROIs are reported in [Inline Supplementary Table 1](#). Based on the findings, uncorrected for multiple comparisons, we observed an association between NSS and GM volume in the left and right temporal poles ($r = 0.256$, $P_{\text{uncorr}} = 0.023$, and $r = 0.242$, $P_{\text{uncorr}} = 0.032$, respectively), left Heschl's sulcus ($r = 0.318$, $P_{\text{uncorr}} = 0.004$), right anterior insula ($r = 0.243$, $P_{\text{uncorr}} = 0.031$), as well as the left and right hippocampi ($r = 0.272$, $P_{\text{uncorr}} = 0.015$, and $r = 0.258$, $P_{\text{uncorr}} = 0.022$, respectively). In all structures, a larger GM corresponded to a larger NSS. [Fig. 2](#) illustrates the correlations observed in the cortical structures, whereas [Fig. 3](#) shows the correlation of NSS with hippocampal GM volume.

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.

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 with higher noise sensitivity. The Heschl's sulcus is adjacent to Heschl's gyrus, which contains the primary auditory cortex ([Abdul-Kareem and Sluming, 2008](#)). Pre-existent as well as training-induced differences in the morphology of Heschl's gyrus are shown to relate to its function ([Schneider et al., 2002](#); [Warrior et al., 2009](#)). We can assume that the volumetric differences that we observed in this area have a relationship to an altered auditory processing in noise sensitivity. Accordingly, diminished abilities for sensory gating and discrimination of sound noisiness in noise-sensitive individuals were demonstrated in recent electrophysiological studies ([Kliuchko et al., 2016](#); [Shepherd et al., 2016](#)). Remarkably, we found that the volume of Heschl's sulcus was related to noise sensitivity only in the left hemisphere. The function of the primary auditory cortex is functionally separated in terms of its involvement with spectro-temporal processing where the right hemisphere mostly attributed with spectral processing and the left hemisphere with temporal processing ([Zatorre et al., 2002](#)). It is also proposed that the functional asymmetry of the auditory cortex is related to asymmetry in temporal sampling ([Poeppel, 2003](#)). According to this view, the left hemisphere is recruited in processing rapid acoustic changes in temporal integration 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 ([Warrior 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 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 cognitive functions, one of which is an integration of higher-order processed stimuli and perceived events with emotions ([Olson et al., 2007](#)). Functional studies have indicated the temporal pole to be involved in emotion, especially with self-induced states of sadness, anxiety, and happiness ([Kimbrell et al., 1999](#); [Pelletier et al., 2003](#)). The temporal pole is connected within secondary and associative auditory areas in the temporal lobe. Moreover, it is highly interconnected with the amygdala and receives inputs from the insular cortex ([Olson et al., 2007](#); [Pascual et al., 2015](#)). Notably, the temporal pole is functionally connected with the hippocampus ([Pascual et al., 2015](#)), which, too, showed a bilateral positive association of its GM volume and noise sensitivity in our study. Besides the auditory system, the temporal pole receives input from visual and olfactory systems and serves as a structure of sensory-emotional coupling for these modalities as well ([Olson et al., 2007](#)). The activation of the temporal pole induced by auditory, visual, or olfactory information seems to follow a dorsal/ventral segregation with auditory stimuli activating its dorsal part ([Olson et al., 2007](#)). However, the parcellation approach used in our study did not allow us to determine more precisely which part of the temporal pole was specifically enlarged. Some studies report that 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. The primary role of the hippocampus is related to memory and learning; however, it has been reported to participate in the processing of the emotional content of music (Mitterschiffthaler et al., 2007) and identification of stimulus novelty (Lieberman et al., 2009; Thoma et al., 2008) 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 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 processing (Phelps, 2004). Hippocampal volume is related to awareness of the relation between a conditional and an unconditional stimulus and thus demonstrates that the relative volume of the bilateral hippocampus in healthy people moderates aversive learning (Cacciaglia et al., 2014). Considering the observed relationship between volumes of the left and right hippocampus and noise sensitivity score, we may speculate that noise sensitivity is related to the ability to form the associations between negative emotional experience and noise.

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).

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

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 system. However, the results did not reveal an association between amygdala's volume and noise

sensitivity. Despite the lack of the structural differences found, it remains an open question whether noise sensitivity is related to the amygdalar function. An fMRI study of tinnitus revealed that the amygdala was activated in response to pleasant and unpleasant 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 activated during the presentation of negative emotional stimuli (Carpenter-Thompson et al., 2014). Perhaps, similarly to tinnitus patients, noise-sensitive persons employ an alternative strategy for affective processing. Moreover, in an fMRI study of emotion perception in sensory processing sensitivity (SPS; Aron et al., 2012), which is a trait determining high responsiveness to environmental and social stimuli, the amygdala's activation did not differentiate highly sensitive persons from non-sensitive ones (Acevedo et al., 2014). However, the activation of the insula in response to emotional stimuli increased as a function of SPS. Based on these observations, Acevedo et al. (2014) suggested that SPS is not related to attributing emotion to sensory stimuli, but to a greater sensitivity to inner and outer 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 sensitivity are use-dependent. However, we cannot rule out a potential contribution of genetic factors. Perhaps, noise-sensitive individuals are born with a predisposition for larger volumes of the primary auditory cortex, anterior insula, and hippocampus, leading them to be more prone to evaluate aversively environmental (auditory) stimuli. Noise sensitivity has 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 called Williams syndrome, in which noise sensitivity is often comorbid, there is a structural and functional augmentation of the left auditory cortex that cannot be explained by training but by genetics (Wengenroth et al., 2010). Hence, at least in a clinical population, it is possible that structural brain differences are pre-existent. Whether this could be the case for noise-sensitive but healthy individuals is a question requiring further investigation.

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.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.neuroimage.2017.11.041>.

References

- Abdalla, C.G., Geha, P., 2017. Chronic pain and chronic stress: two sides of the same coin? *Chronic Stress* 1, 1–10.
- Abdul-Kareem, I.A., Sluming, V., 2008. Heschl gyrus and its included primary auditory cortex: structural MRI studies in healthy and diseased subjects. *J. Magn. Reson. Imaging* 28, 287–299.
- Acevedo, B.P., Aron, E.N., Aron, A., Sangster, M.D., Collins, N., Brown, L.L., 2014. The highly sensitive brain: an fMRI study of sensory processing sensitivity and response to others' emotions. *Brain Behav.* 4, 580–594.
- Aron, E.N., Aron, A., Jagiellowicz, J., 2012. Sensory processing sensitivity: a review in the light of the evolution of biological responsiveness. *Personal. Soc. Psychol. Rev.* 16, 262–282.
- Barrett, L.F., Quigley, K.S., Bliss-Moreau, E., Aronson, K.R., 2004. Interoceptive sensitivity and self-reports of emotional experience. *J. Pers. Soc. Psychol.* 87, 684–697.
- Basner, M., Babisch, W., Davis, A., Brink, M., Clark, C., Janssen, S., Stansfeld, S.A., 2014. Auditory and non-auditory effects of noise on health. *Lancet* 383, 1325–1332.
- Blankstein, U., Chen, J., Diamant, N.E., Davis, K.D., 2010. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. *Gastroenterology* 138, 1783–1789.
- Bordi, F., LeDoux, J., 1992. Sensory tuning beyond the sensory amygdala: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. *J. Neurosci.* 12, 2493–2503.
- Burunat, L., Brattico, E., Puoliväli, T., Ristaniemi, T., Sams, M., Toivaiainen, P., Snyder, J., 2015. Action in perception: prominent visuo-motor functional symmetry in musicians during music listening. *PLoS One* 10, 1–18.
- Burunat, L., Tsatsishvili, V., Brattico, E., Toivaiainen, P., 2017. Coupling of action-perception brain networks during musical pulse processing: evidence from region-of-interest-based independent component analysis. *Front. Hum. Neurosci.* 11, 230.
- Cacciaglia, R., Pohlack, S.T., Flor, H., Nees, F., 2014. Dissociable roles for hippocampal and amygdalar volume in human fear conditioning. *Brain Struct. Funct.* 220, 2575–2586.
- Carpenter-Thompson, J.R., Akrofi, K., Schmidt, S.A., Dolcos, F., Husain, F.T., 2014. Alterations of the emotional processing system may underlie preserved rapid reaction time in tinnitus. *Brain Res.* 1567, 28–41.
- Craig, A.D., 2009. How do you feel — now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70.
- Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195.
- Cromwell, H.C., Mears, R.P., Wan, L., Boutros, N.N., 2008. Sensory gating: a translational effort from basic to clinical science. *Clin. EEG Neurosci.* 39, 69–72.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis I: segmentation and surface reconstruction. *Neuroimage* 9, 179–194.
- Damasio, A.R., 2004. Emotions and feelings. In: Manstead, A.S.R., Frijda, N., Fischer, A. (Eds.), *Feelings and Emotions: the Amsterdam Symposium*. Oxford University Press, Cambridge, UK, pp. 49–57.
- Destrieux, C., Fischl, B., Dale, A.M., Halgen, E., 2010. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 53, 1–15.
- Dunn, B.D., Stefanovitch, I., Evans, D., Oliver, C., Hawkins, A., Dalgleish, T., 2010. Can you feel the beat? Interoceptive awareness is an interactive function of anxiety- and depression-specific symptom dimensions. *Behav. Res. Ther.* 48, 1133–1138.
- Ellermeier, W., Eigenstetter, M., Zimmer, K., 2001. Psychoacoustic correlates of individual noise sensitivity. *J. Acoust. Soc. Am.* 109, 1464–1473.
- Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9, 195–207.
- Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., Pitman, R.K., 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat. Neurosci.* 5, 1242–1247.
- Gold, B.P., Frank, M.J., Bogert, B., Brattico, E., 2013. Pleasurable music affects reinforcement learning according to the listener. *Front. Psychol.* 4, 541.
- Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B., 2016. Tinnitus-related distress: evidence from fMRI of an emotional stroop task. *BMC Ear. Nose. Throat Disord.* 16, 10.
- Griffiths, T.D., Warren, J.D., 2002. The planum temporale as a computational hub. *Trends Neurosci.* 25, 348–353.
- Haller, S., Birbaumer, N., Veit, R., 2010. Real-time fMRI feedback training may improve chronic tinnitus. *Eur. Radiol.* 20, 696–703.
- Heinonen-Guzejev, M., 2008. Noise Sensitivity – Medical, Psychological and Genetic Aspects. University of Helsinki.
- Heinonen-Guzejev, M., Jauhainen, T., Vuorinen, H.S., Vilijanen, A., Rantanen, T., Koskenvuo, M., Heikkilä, K., Mussalo-Rauhamaa, H., Kaprio, J., 2011. Noise sensitivity and hearing disability. *Noise Health* 13, 51–58.
- Heinonen-Guzejev, M., Vuorinen, H.S., Mussalo-Rauhamaa, H., Heikkilä, K., Koskenvuo, M., Kaprio, J., 2005. Genetic component of noise sensitivity. *Twin Res. Hum. Genet.* 8, 245–249.
- Herry, C., Bach, D.R., Esposito, F., Di Salle, F., Perrig, W.J., Scheffler, K., Lüthi, A., Seifritz, E., 2007. Processing of temporal unpredictability in human and animal amygdala. *J. Neurosci.* 27, 5958–5966.
- Job, R.F.S., 1999. Noise sensitivity as a factor influencing human reaction to noise. *Noise Health* 1, 57–68.
- Kimbrell, T.A., George, M.S., Parekh, P.I., Ketter, T.A., Podell, D.M., Danielson, A.L., Repella, J.D., Benson, B.E., Willis, M.W., Herscovitch, P., Post, R.M., 1999. Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biol. Psychiatry* 46, 454–465.
- Kleber, B., Friberg, A., Zeitouni, A.G., Zatorre, R.J., 2017. Experience-dependent modulation of right anterior insula and sensorimotor regions as a function of noise-masked auditory feedback in singers and nonsingers. *Neuroimage* 147, 97–110.
- Kleber, B., Zeitouni, A.G., Friberg, A., Zatorre, R.J., 2013. Experience-dependent modulation of feedback integration during singing: role of the right anterior insula. *J. Neurosci.* 33, 6070–6080.
- Kliuchko, M., 2017. Noise Sensitivity in the Function and Structure of the Brain. University of Helsinki.
- Kliuchko, M., Heinonen-Guzejev, M., Monacis, L., Gold, B.P., Heikkilä, K.V., Spinoza, V., Tervaniemi, M., Brattico, E., 2015. The association of noise sensitivity with music listening, training, and aptitude. *Noise Health* 17, 350–357.
- Kliuchko, M., Heinonen-Guzejev, M., Vuust, P., Tervaniemi, M., Brattico, E., 2016. A window into the brain mechanisms associated with noise sensitivity. *Sci. Rep.* 6, 39236.
- Kraus, K.S., Canlon, B., 2012. Neuronal connectivity and interactions between the auditory and limbic systems. *Eff. noise tinnitus. Hear. Res.* 288, 34–46.
- Kumar, S., Tansley-Hancock, O., Sedley, W., Winston, J.S., Callaghan, M.F., Allen, M., Cope, T.E., Gander, P.E., Bamiou, D.-E., Griffiths, T.D., 2017. The brain basis for misophonia. *Curr. Biol.* 27, 1–7.
- Kumar, S., von Kriegstein, K., Friston, K., Griffiths, T.D., 2012. Features versus feelings: dissociable representations of the acoustic features and valence of aversive sounds. *J. Neurosci.* 32, 14184–14192.
- Lazar, S.W., Kerr, C.E., Wasserman, R.H., Gray, J.R., Douglas, N., Treadway, M.T., Mcgarvey, M., Quinn, B.T., Dusek, J. a., 2005. Meditation experience is associated with increased cortical thickness. *Neuroreport* 16, 1893–1897.
- Leaver, A.M., Seydell-Greenwald, A., Turesky, T.K., Morgan, S., Kim, H.J., Rauschecker, J.P., 2012. Cortico-limbic morphology separates tinnitus from tinnitus distress. *Front. Syst. Neurosci.* 6, 21.
- Lemaitre, H., Godman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and grey matter volume? *Neurobiol. Aging* 33, 617 e1–617.e9.
- Liberman, T., Velluti, R.A., Pedemonte, M., 2009. Temporal correlation between auditory neurons and the hippocampal theta rhythm induced by novel stimulations in awake Guinea pigs. *Brain Res.* 1298, 70–77.
- Lindborg, P., Friberg, A., 2016. Personality traits bias the perceived quality of sonic environments. *Appl. Sci.* 6, 405.
- Lodhia, V., Brock, J., Johnson, B.W., Hautus, M., 2014. Reduced object related negativity response indicates impaired auditory scene analysis in adults with autistic spectrum disorder. *PeerJ* 2, e261.
- Marsh, R.A., Fuzessery, Z.M., Grose, C.D., Wenstrup, J.J., 2002. Projection to the inferior colliculus from the basal nucleus of the amygdala. *J. Neurosci.* 22, 10449–10460.
- Mitterschiffthaler, M.T., Fu, C.H.Y., Dalton, J.A., Andrew, C.M., Williams, S.C.R., 2007. A functional MRI study of happy and sad affective states induced by classical music. *Hum. Brain Mapp.* 28, 1150–1162.
- Mohedano-Moriano, A., Pro-Sistiaga, P., Arroyo-Jimenez, M.M., Artacho-Péruela, E., Insausti, A.M., Marcos, P., Cebada-Sánchez, S., Martínez-Ruiz, J., Muñoz, M., Blaizot, X., Martínez-Marcos, A., Amaral, D.G., Insausti, R., 2007. Topographical and laminar distribution of cortical input to the monkey entorhinal cortex. *J. Anat.* 211, 250–260.
- Olson, I.R., Plotzker, A., Ezzyat, Y., 2007. The Enigmatic temporal pole: a review of findings on social and emotional processing. *Brain* 130, 1718–1731.
- Pascual, B., Masdeu, J.C., Hollenbeck, M., Makris, N., Insausti, R., Ding, S.L., Dickerson, B.C., 2015. Large-scale brain networks of the human left temporal pole: a functional connectivity MRI study. *Cereb. Cortex* 25, 680–702.
- Pelletier, M., Bouthillier, A., Levesque, J., Carrier, S., Breault, C., Paquette, V., Mensour, B., Leroux, J.-M., Beaudoin, G., Bourgouin, P., Beauregard, M., 2003. Separate neural circuits for primary emotions? Brain activity during self-induced sadness and happiness in professional actors. *Neuroreport* 14, 9370–9370.
- Persson, R., Björk, J., Ardö, J., Albin, M., Jakobsson, K., 2007. Trait anxiety and modeled exposure as determinants of self-reported annoyance to sound, air pollution and other environmental factors in the home. *Int. Arch. Occup. Environ. Health* 81, 179–191.
- Phelps, E.A., 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* 14, 198–202.
- Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. *Nat. Neurosci.* 4, 437–441.
- Poeppel, D., 2003. The analysis of speech in different temporal integration windows: cerebral lateralization as asymmetric sampling in time. *Speech Commun.* 41, 245–255.
- Pollatos, O., Gramann, K., Schandry, R., 2007. Neural systems connecting interoceptive awareness and feelings. *Hum. Brain Mapp.* 28, 9–18.
- Rojas, D.C., Bawn, S.D., Benkers, T.L., Reite, M.L., Rogers, S.J., 2002. Smaller left hemisphere planum temporale in adults with autistic disorder. *Neurosci. Lett.* 328, 237–240.
- Schirmer-Mokwa, K.L., Fard, P.R., Zamorano, A.M., Finkel, S., Birbaumer, N., Kleber, B., 2015. Evidence for enhanced interoceptive accuracy in professional musicians. *Front. Behav. Neurosci.* 9, 349.
- Schneider, P., Scherg, M., Dosch, H.G., Specht, H.J., Gutschalk, A., Rupp, A., 2002. Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nat. Neurosci.* 5, 688–694.
- Shepherd, D., Hautus, M., Lee, S.Y., Mulgrew, J., 2016. Electrophysiological approaches to noise sensitivity. *J. Clin. Exp. Neuropsychol.* 3395, 1–13.
- Shepherd, D., Heinonen-Guzejev, M., Heikkilä, K., Dirks, K., Hautus, M., Welch, D., McBride, D., 2015. The negative affect hypothesis of noise sensitivity. *Int. J. Environ. Res. Public Health* 12, 5284–5303.

- Stansfeld, S.A., 1992. Noise, noise sensitivity and psychiatric disorder: epidemiological and psychophysiological studies. *Psychol. Med.* 22, 1–44.
- Stansfeld, S.A., Clark, C.R., Turpin, G., Jenkins, L.M., Tarnopolsky, A., 1985. Sensitivity to noise in a community sample: II. Measurement of psychophysiological indices. *Psychol. Med.* 15, 255–263.
- Stansfeld, S.A., Matheson, M.P., 2003. Noise pollution: non-auditory effects on health. *Br. Med. Bull.* 68, 243–257.
- Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J.L., Resnick, S.M., 2010. Longitudinal changes in cortical thickness associated with normal aging. *Neuroimage* 52, 1215–1223.
- Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. *J. Affect. Disord.* 61, 201–216.
- Thoma, R.J., Hanlon, F.M., Petropoulos, H., Miller, G.A., Moses, S.N., Smith, A., Parks, L., Lundy, S.L., Sanchez, N.M., Jones, A., Huang, M., Weisend, M.P., Canive, J.M., 2008. Schizophrenia diagnosis and anterior hippocampal volume make separate contributions to sensory gating. *Psychophysiology* 45, 926–935.
- Toga, A.W., Thompson, P.M., Sowell, E.R., 2011. Mapping brain maturation. *Trends Neurosci.* 29, 148–159.
- Van Der Loo, E., Congedo, M., Vanneste, S., Van de Heyning, Van, P., De Ridder, D., 2011. Insular lateralization in tinnitus distress. *Auton. Neurosci. Basic Clin.* 165, 191–194.
- van Kamp, I., Job, R.F.S., Hatfield, J., Haines, M., Stellato, R.K., Stansfeld, S.A., 2004. The role of noise sensitivity in the noise–response relation: a comparison of three international airport studies. *J. Acoust. Soc. Am.* 116, 3471.
- Vanneste, S., Plazier, M., der Loo, Van de Heyning, E., Van, P., Congedo, M., De Ridder, D., 2010. The neural correlates of tinnitus-related distress. *Neuroimage* 52, 470–480.
- Warrier, C., Wong, P., Penhune, V., Zatorre, R.J., Parrish, T., Abrams, D., Kraus, N., 2009. Relating structure to function: Heschl's gyrus and acoustic processing. *J. Neurosci.* 29, 61–69.
- Watson, D., Clark, L.A., 1984. Negative affectivity: the disposition to experience aversive emotional states. *Psychol. Bull.* 96, 465.
- Weinstein, N.D., 1978. Individual differences in reactions to noise: a longitudinal study in a college dormitory. *J. Appl. Psychol.* 63, 458–466.
- Wengenroth, M., Blatow, M., Bendszus, M., Schneider, P., 2010. Leftward lateralization of auditory cortex underlies holistic sound perception in Williams syndrome. *PLoS One* 5, 1–10.
- Zatorre, R.J., Belin, P., Penhune, V.B., 2002. Structure and function of auditory cortex: music and speech. *Trends Cogn. Sci.* 6, 37–46.
- Zheng, J., Andreson, K.L., Leal, S., Shestzuk, A., Gulsen, G., Mnatsakanyan, L., Vadera, S., Hsu, F.P.K., Yassa, M.A., Knight, R.T., Lin, J.J., 2017. Amygdala-hippocampal dynamics during salient information processing. *Nat. Commun.* 8, 14413.