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Functional magnetic resonance imaging of tinnitus

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General conclusions

7.1 Introduction

In this thesis, the phenomenon of subjective tinnitus was studied with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). First, experimental paradigms suitable for imaging methods were discussed as well as the results that were generated using these paradigms. Second, two distinct forms of tinnitus were studied. The first was lateralized tinnitus where subjects perceive tinnitus at one side of the head, predominantly at one side of the head or centrally located 'in the head'. The second 'type' of tinnitus was somatic tinnitus, a phenomenon that refers to somatosensory maneuvers that elicit or modulate the psycho-acoustical attributes of tinnitus (e.g., the loudness or pitch of the tinnitus). In the following paragraphs the main findings will be discussed and further speculated on in relation to hypotheses of tinnitus generation.

7.2 Experimental paradigms on functional imaging methods of subjective tinnitus

Neuroimaging methods like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) measure signals that presumably reflect the firing rates of multiple neurons and are assumed to be sensitive to changes in the level of neural activity. Both imaging modalities depend on the hemodynamic or vascular response to neural activity. They may identify changes in local neural activity that result from induced modulation of tinnitus and, in some cases, may identify abnormal steady-state activity associated with tinnitus.

The spatial and temporal resolution limit the use of these methods to the investigation of the rather slow hemodynamic responses. These can be identified in brain areas, summarizing responses of a large number of neurons. In addition, these methods only measure the strength of activity. Changes in, for example, neural synchrony that have also been suggested to relate to tinnitus (see e.g. [Eggermont \(2007a\)](#)) presumably remain unnoticed when the brain is studied with PET or fMRI.

In addition, changes in spontaneous activity—another marker of tinnitus, is not measured with blood oxygen level dependent (BOLD) fMRI since it only measures differences between conditions and cannot be used to assess baseline levels of activity. Some PET methods however have been used to study steady state neural activity in subjects with tinnitus and in subjects without tinnitus.

Nevertheless, there are two basic paradigms that have been applied in functional neuroimaging of tinnitus. Firstly, sound-evoked responses as well as steady state neural activity have been measured to compare patients with tinnitus to healthy controls. Secondly, paradigms that involve modulation of tinnitus by a controlled stimulus allow for a within-subject comparison that identifies neural activity that may be correlated to the tinnitus percept.

Even though there are many differences across studies, the general trend emerging from the neuroimaging studies, is that tinnitus in humans may correspond to enhanced neural activity across several centers of the central auditory system. Also, neural activity in non-auditory areas including frontal areas, the limbic system and the cerebellum seems to be associated with the perception of tinnitus. These results indicate that in addition

to the auditory system, non-auditory systems may represent a neural correlate of tinnitus. The studies reviewed in chapter 2 suggest abnormal neural activity in tinnitus patients at several levels in the brain. Specifically, cortical and sub-cortical auditory brain areas show a correlation between blood flow and tinnitus loudness. However, in many cases, it is unclear to what extent the abnormalities truly relate to tinnitus. Some aspects may also be related to hearing loss or hyperacusis, rather than tinnitus. Also, the presented differences between subject groups may have been confounded to differences in matching criteria between groups (e.g., hearing levels and age).

Although the currently published neuroimaging studies typically show a correspondence between tinnitus and enhanced neural activity, it will be important to perform future studies on subject groups that are closely matched for characteristics such as age, gender and especially hearing loss in order to rule out the contribution of these factors to the abnormalities specifically ascribed to tinnitus.

The observation that tinnitus corresponds to abnormal neural activity in auditory brain areas is not very surprising. After all, tinnitus is the abnormal percept of sound. The question remains as to how the abnormalities emerge. To what extent does the abnormal activity in the auditory cortex, which presumably has a close correspondence to the tinnitus percept, reflect an inherent abnormality of the cortex? In other words, does it reflect pathology of the cortex or is it a consequence of an abnormal interaction with subcortical brain areas and possibly limbic or frontal regions? And how does the abnormality simply reflect the consequence of peripheral hearing loss? These questions remain to be answered and the answers are key in understanding the pathology of tinnitus.

7.3 Increased sound evoked responses in subjects with unilateral tinnitus

Chapter 3 shows the results of a study on sound-evoked responses as a marker of tinnitus. Based on the lateralization of the tinnitus in a subgroup of patients we expected to measure a lateralization in the responses in the central auditory system that would reflect the lateralization of the tinnitus.

The results show an increased sound-evoked response of the inferior colliculi (IC) of subjects with lateralized tinnitus when compared to those in subjects without tinnitus (see figure 3.4), which is in close agreement with [Salvi *et al.* \(1990\)](#) who measured enhanced evoked response amplitudes in the inferior colliculus of the chinchilla following acoustic trauma. The responses in the auditory cortex (combining primary and secondary auditory cortices) however were not different between the subject groups.

As can be observed in the auditory cortex (see figure 3.3), contralateral stimuli gave a larger response than ipsilateral stimuli. We also found an intensity dependency, i.e., stimuli of 70 dB (SPL) gave a larger response than stimuli of 40 dB (SPL). In the control group we found a functional asymmetry as described earlier ([Devlin *et al.*, 2003](#); [Krumbholz *et al.*, 2005](#)). In the inferior colliculi of subjects with tinnitus we observed a change in this asymmetry; subjects with tinnitus showed no clear contralateral dominance in the strength of the responses. So, in addition to the change in the level of the sound-evoked responses

we also observed a difference in response lateralization.

7.4 Changes in lateralization and connectivity patterns in subjects with unilateral tinnitus

Based on the main results described in chapter 3 (increased sound-evoked responses and changes in the response lateralization in the inferior colliculi of subjects with tinnitus), more subjects were included in the study. The strength and lateralization of sound-evoked responses and the connectivity patterns between nuclei in the auditory pathway were assessed and the results were described in chapter 4. However, there was no dependency of the strength of the sound-evoked response on the side of the tinnitus. This is in line with previous work (Lanting *et al.*, 2008) and was also confirmed by a recent paper of Melcher *et al.* (2009) showing that the lateralization of the tinnitus is not reflected in the strength of the evoked responses in the IC. The other studies that did show a relation between tinnitus lateralization and brain activity, either did not match their subject groups based on e.g. hearing loss (Kovacs *et al.*, 2006; Smits *et al.*, 2007), or had ongoing background noise that might have saturated neural responses (Melcher *et al.*, 2000). This presumably caused changes in the lateralization of the brain responses. In summary, the laterality of the tinnitus did not correspond to a lateralized change in the neural response to sound.

The vermis of the cerebellum responded significantly stronger in the patient group compared to the controls. The role of the vermis of the cerebellum is not known, but several authors discussed its role. Lesions in the vermis of the cerebellum in rats have been reported to block the long-term habituation of the acoustic startle response (Leaton and Supple, 1991). Also, in humans, the medial part of the cerebellum is important in the long-term habituation of the acoustic startle response (Timmann *et al.*, 1998; Maschke *et al.*, 2000). A meta analysis, summarizing the findings of fifteen studies on the neural correlates of active and passive listening, reported a general role of the cerebellum in auditory processing (Petacchi *et al.*, 2005).

The vermis of the cerebellum was suggested to play a role in lateral gaze, which in particular subjects with tinnitus changed the perceived loudness of the tinnitus (Lockwood *et al.*, 2001). We can speculate about the possible relation of these results to ours: one could suggest that the habituation of the continuous percept of tinnitus might be impaired in these patients, leading to the prolonged complaints of tinnitus. The vermis of the cerebellum might thus not directly relate to the percept but might influence the habituation to perceived sounds—in this case tinnitus. Nevertheless, given our data, we cannot draw any firm conclusion about the cerebellum, except pointing out that it shows a larger response to sound in patients with tinnitus as compared to controls.

Further region of interest (ROI) analysis showed that, at many levels in the auditory pathway, there were no differences in the strength of the response between subject groups. In general, nuclei of the auditory pathway showed a stronger response to 70 dB (SPL) stimuli than to 40 dB stimuli. In addition, the auditory pathway showed stronger responses to contralateral stimuli—with the exception of the cochlear nucleus (CN), which responded most strongly to ipsilateral stimuli. The pattern of responses to the sound stim-

uli was deviating between the subject groups in only two cases: the right primary auditory cortex (PAC) and the right IC. Here, in the patient group, there was a reduced difference between ipsilateral and contralateral stimuli. This could also be observed by looking solely to the lateralization index, which was significantly lower in these same nuclei (right IC and PAC). Interestingly, the patients lateralization was lower in almost all nuclei and was significant lower when performing a repeated measures ANOVA on all right-hemisphere nuclei, except the CN. Unilateral tinnitus thus relates to a decreased lateralization of the auditory pathway. This decreased lateralization might relate to a diminished efficiency in the inhibitory ipsilateral input to the IC (see figure 4.10). Disinhibition could effectively lead to a more equal input from both ears (via contralateral excitatory input and a dysfunctional inhibition from the ipsilateral ear, see [Ehret and Romand \(1997\)](#)) and therefore decrease the lateralization index.

In contrast to our earlier work (chapter 3) and a recent article by [Melcher *et al.* \(2009\)](#), the results in chapter 3 indicate that the IC of the patients does not show increased sound-evoked responses. It did in the subjects that we studied earlier but we were not able to replicate this finding here, with a larger group of subjects. The fact that the tinnitus subjects were, on average, 10 years older than the controls and the difference in auditory stimuli (binaural stimuli vs. monaural stimuli) might influence our findings. Also the methodological difference in the selection of voxels might have an influence, although there is little evidence for that.

The last part of chapter 4 described connectivity patterns between nuclei of the auditory pathway, with in addition the vermis of the cerebellum. We adopted two distinctive forms of connectivity analysis in this work ([Horwitz, 2003](#)). In addition to the simple (Pearson) cross-correlation as a measure for functional connectivity ([Friston, 1994](#)) we studied partial cross-correlation as measure for effective connectivity ([Marrelec *et al.*, 2006, 2007, 2009](#)). By using partial correlation, mutual characteristics like sound-evoked responses or other task-related features are taken out leaving an inherent measure of effective connectivity.

We observed that for all connections between elements in the model, the Pearson correlation was higher than the partial correlation, indicating that much of the correlation could be driven by the experimental paradigm. We assessed the normal connectivity patterns and observed high partial correlation coefficients between the ipsilateral PAC and auditory association cortex (AAC). Also, in subjects with tinnitus, the partial correlation coefficient between the left AAC and the vermis of the cerebellum was increased; indicating that the cerebellum appears to show effective connectivity with the auditory association cortex. We also found differences in connectivity in patients with tinnitus based on permutation testing procedures. Specifically, the effective connectivity was disturbed between the IC and the contralateral medial geniculate body (MGB), as well as between the left CN and the left PAC.

In conclusion, we did not find tinnitus related differences in the strength of response to sound in the auditory pathway. Yet, we did find changes in lateralization and connectivity, especially from the IC to the contralateral MGB. Apparently, tinnitus is somehow related to changes in connectivity patterns, which may lead to a change in lateralization. The role of the cerebellum in tinnitus remains unknown, although it shows a stronger response to

sound in patients with unilateral tinnitus, compared to subjects without tinnitus.

7.5 Neural correlates of somatosensory modulation of tinnitus

Somatic tinnitus is a phenomenon which refers to tinnitus that is elicited or modulated by somatosensory input. This may be a specific form of multimodal integration. The study in chapter 5 demonstrates that overlap of somatosensory and auditory input can be measured in the auditory pathway; jaw protrusion caused a response in the auditory system and may explain the influence of jaw protrusion on the perceived loudness of tinnitus. Probability maps can be used to indicate voxels that show functional overlap between unimodal conditions. We found overlap between the auditory modality and the somatosensory modality in the primary auditory cortex (BA 41) and the auditory association cortex (BA 22) (see figure 5.6). Interestingly, the only differences between subject with tinnitus and controls were found in the cochlear nuclei and IC. Jaw protrusion evoked in both ROIs a larger response in subjects with tinnitus compared to those in controls.

At the level of the brainstem there is already integration of somatosensory input and auditory input. The dorsal column-medial lemniscal system and the trigeminal sensory complex are key structures showing modulation of neural activity in the auditory system at the level of the cochlear nucleus and the inferior colliculus. Nuclei of the dorsal column are involved in relaying proprioceptive information from the trunk, shoulders, head (pinna) and posterior neck muscles to the ventral cochlear nucleus and dorsal cochlear nucleus (Shore *et al.*, 2000; Shore and Zhou, 2006). In addition to multimodal integration at the level of the cochlear nuclei and inferior colliculi, there is some evidence for cortical integration of somatosensory input and auditory input. The caudal medial belt area gets indirect and direct somatosensory input and receives auditory input through the anterodorsal division of the medial geniculate complex (Smiley *et al.*, 2007; Hackett *et al.*, 2007a,b).

Our findings, in combination with existing literature stress the importance of somatosensory interaction in the extralemniscal or non-classical auditory system (Møller *et al.*, 1992) in defining possible mechanisms underlying tinnitus. One hypothesis, relating tinnitus to changes in normal somatosensory integration, is that a change in input from the auditory system (due to e.g. noise-induced hearing loss) might influence the somatosensory input to the brainstem and might thus form a neurophysiological basis for modulating perceptual characteristics of tinnitus (Shore *et al.*, 2008). Especially our finding that jaw protrusion shows enhanced responses in the inferior colliculi and cochlear nuclei of subjects with tinnitus compared to controls underlines this hypothesis. It however remains a question what the exact neurophysiologic mechanisms are that may underlie tinnitus itself.

In conclusion, we showed responses to jaw protrusion throughout the auditory pathway. These responses occurred in both tinnitus and control subjects. The somatic responses of the auditory brain areas to jaw protrusion presumably account for the modulation of tinnitus by jaw protrusion. The response to jaw protrusion of the cochlear nuclei and the inferior colliculi was larger in subjects with tinnitus than in healthy controls, suggesting an unusually auditory-somatic interaction in the patient group.

7.6 The auditory pathway – is the limbic system involved?

Chapters 3–5 show the results of fMRI studies on subjective tinnitus. On the other hand, an imaging technique sensitive to diffusion of water in tissue was used in chapter 6: diffusion tensor imaging (DTI). This technique allows us to track anatomical pathways between predefined regions of interest and we specifically assessed part of the auditory pathway. The first interesting result is the ability to track the classical auditory pathway. The tracks that connect the auditory cortex (AC) and the IC all pass through the MGB. Thus, although the MGB was not preselected as a region of interest, these tracks follow the expected pathway of the classical auditory system. Hence, as in a recent validation study performed in the macaque (Dauguet *et al.*, 2007), DTI identifies known neuronal tracks in the brain.

Based on earlier hypotheses (Møller *et al.*, 1992; Jastreboff, 1990) we expected that an anatomical connection between the auditory system and the limbic system would exist and indeed, we found such a connection between the auditory cortex and the amygdala which also connected to the MGB. This suggests that DTI is able to detect an anatomical pathway which is part of the non-classical auditory pathway, e.g., the connection from the dorsal MGB to the limbic system (amygdala).

In order to summarize the track properties, we computed three quantities for each connection in each subject: the fractional anisotropy (FA), the weighted fractional anisotropy (wFA), and the connection strength (S). The anisotropy is a property of each voxel in the brain. It is a measure of the directionality of water diffusion in the voxel. If the water diffusion is primarily in a particular direction, the voxel is assumed to contain neural fibers that are oriented in that direction. A fiber track consists of a large number of neighboring voxels. The average FA of a track is thus assumed to be a measure of the patency of the track.

We assumed that the wFA is an improved measure of this patency, as it takes the probability that a voxel is actually part of the track into account. Obviously, the wFA can only be computed when using probabilistic fiber tracking.

Finally, the connection strength S is the fraction of samples in a seed region that actually reaches the target region. A high strength S is again a measure of the patency of the track. Conversely, a low strength may indicate that the seed region is connected primarily to other end points. Although these three measures (FA, wFA and S) are the result of considerable data reduction, they provide measures that allow for straightforward comparisons between subjects and subject groups.

By quantifying the tracks that pairwise connect the IC, AC and amygdala (AM), we were able to make comparisons between control subjects and tinnitus patients. These three ROIs were selected because they may play an important role in the mechanisms that lead to tinnitus.

Despite the fact that a relation between tinnitus and peripheral hearing loss is present, it is not straightforward. The mechanisms underlying the diffuse relation between hearing loss and tinnitus are unclear. It is possible that subtle characteristics of the functional or anatomical (structural) connectivity of the central auditory systems determine whether a subject develops tinnitus. In addition, non-auditory brain areas are believed to be involved in tinnitus. Specifically, the interaction between the limbic and the auditory system has been proposed in models that explain tinnitus (Lockwood *et al.*, 1998; Jastreboff, 1990;

Møller, 2006a).

Abnormal spontaneous brain rhythms in tinnitus patients are indicative of abnormal functional connectivity in such patients. These brain rhythms reflect the activity of forward and backward loops connecting brain areas, specifically of the cortical-thalamic connections (Llinas *et al.*, 2005). In tinnitus patients, the alpha brain rhythm is reduced, while the delta rhythm is substantially enhanced (Weisz *et al.*, 2005a). These abnormal brain rhythms, which differentiate tinnitus patients from control subjects, could in part be due to differences in the anatomical connections.

Our study is an attempt to show possible anatomical differences between subject groups using DTI. The computation of FA, wFA and S allowed us to compute such differences. We found differences and similarities between tinnitus patients and healthy controls. For example, the variability across subjects for FA and wFA of the paths was remarkably small within each group, and was also very similar between both groups.

Significant differences in path strength between tinnitus patients and healthy controls were found for the left IC-AM connection, the right AC-IC connection, and the AC-AM connection for both hemispheres, which also resulted in a significant difference for the lateralization. Tinnitus patients also showed a higher FA in the AM-AC connection.

Regarding lateralization, differences between tinnitus patients and controls were found for the FA of the AC-AM connection and the weighted FA of the AC-AM and IC-AC connections. This result may correspond to the abnormal lateralization in brain function observed in tinnitus patients in a PET study (see chapter 4).

The difference in strength of the connection between auditory cortex and amygdala in subjects with tinnitus compared to controls indicates that the limbic system may indeed play a major role in tinnitus, especially concerning the emotional content of the percept of tinnitus. Although cognitive therapies, focused on treating tinnitus by habituation, have been used for many years (Jastreboff and Jastreboff, 2003; Jastreboff, 2007), no imaging study prior to the present one has shown a potential anatomical pathway that might function differently between tinnitus patients and normal hearing controls.

7.7 Conclusions and outlook

In this work we found evidence linking tinnitus to the central auditory system. We found increased sound-evoked responses in a subset of subjects with lateralized tinnitus (chapter 3) while it was absent in another subset (chapter 4). This could reflect a 'hidden variable' like hyperacusis that may be present in some patients but not all. The increased sound-evoked activity might thus not necessarily be a marker of tinnitus but could as well be a marker for a phenomenon that in many cases accompanies tinnitus (i.e., hyperacusis).

Additionally we found evidence for a change in response lateralization and connectivity at the level of the midbrain (i.e., the inferior colliculus) in subjects with tinnitus. As suggested earlier (Møller, 2006c), a change in the balance between excitation and inhibition could not only lead to a change in the 'gain-setting' of the auditory pathway (Salvi *et al.*, 2000), but also lead to a change in the response lateralization (chapter 4).

A change in the balance between excitation and inhibition not only affects the auditory pathway but may also affect normal somatosensory-auditory integration. A recent study

has shown that reduced input to the auditory system (due to e.g. hearing loss) affected the level of somatosensory input at the level of brainstem (Shore *et al.*, 2008). In chapter 5 we investigated somatic tinnitus and found increased levels of response to jaw protrusion at the level of the cochlear nucleus in subjects with tinnitus compared to controls. A disturbance in the normal integration might be the basis for the somatosensory modulation of the loudness of tinnitus while the integration is not disturbed in subjects without tinnitus.

Chapter 6 explores the use of DTI to study tinnitus. The difference in strength of the connection between auditory cortex and amygdala in subjects with tinnitus compared to controls, indicates that the limbic system may indeed play a major role in tinnitus, especially concerning the emotional content of the percept of tinnitus.

Yet, there are many ways in which tinnitus can be studied. Functional MR imaging techniques have, for example, a limited temporal resolution (especially when performing auditory experiments using a sparse design). One of the hypothesized basis aspects of tinnitus—in addition to the increased spontaneous neural activity—corresponds to an increase in neural synchrony (Seki and Eggermont, 2003). One might think of studies that specifically try to assess this synchrony by using EEG or MEG techniques. Also, specific fMRI analysis methods like blind source separation techniques (Langers, 2009) may offer valuable information about brain dynamics for which standard GLM approaches like the ones used in this thesis are not suitable.

So, although this PhD thesis reports evidence for involvement of the central auditory system in tinnitus, it is by far conclusive. Therefore I would like to end this thesis by quoting Frank Herbert

“The beginning of knowledge is the discovery of something we do not understand.”
— Frank Herbert (1920–1986)

and conclude that there is a lot we do not understand about tinnitus and the brain.