Neuromagnetic Investigation of Transient Tinnitus

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Abbreviations

ACC	Anterior Cingulate Cortex
AEF	Acoustically Evoked Magnetic Fields
ECG	Electro-Cardiogram
EOG	Electro-Ocolugram
ICA	Independent Component Analyses
LFP	Local Field Potential
NNCC	Neural Network Correlate of Consciousness
MEG	Magnetencephalography
PFC	Prefrontal Cortex
PTS	Persistent Threshold Shift
SFR	Spontaneous Firing Rate
SNR	Signal Noise Ratio
TTS	Temporary Threshold Shift

Abstract

Tinnitus is defined by an auditory perception in absence of an external source of sound. In this study, global changes in central processing, accompanying *transient* tinnitus and temporary hearing loss, were investigated in humans.

We invited therefore 10 members of rock bands after band practice and assessed a wide range of audiometrical and neuromagnetic data, which were compared to a control condition, without prior exposure to high sound levels.

Data analyses revealed in tinnitus condition power increases for high gamma band activity (55-85Hz) in the right auditory cortex and for alpha- (8-12Hz), slow wave- (2-6Hz) and low gamma (25-45Hz) band activity in the right precuneus. Other than in patients with chronic tinnitus, no decrease of alpha band activity was found in the auditory cortex.

Additional correlation tests were calculated for neuromagnetic and audiometrical data, revealing a relationship for tinnitus intensity and alpha band activity in the left prefrontal cortex and for low gamma band activity and tinnitus intensity in the right posterior cingulum. Effects in the precuneus, the prefrontal cortex and the right posterior cingulum suggest the involvement of attentional and emotional processes in in tinnitus perception.

Analyses of audiometrical data revealed, that in the right ear frequencies at which hearing loss was pronounced, were more likely to be rated as being part of the tinnitus spectrum and that sensitivity to sounds increased with the total amount of years, participants played their instruments.

1. Introduction

Tinnitus is described as an auditory perception in absence of an external source of sound. Approximately 5 -15% of the population suffer from tinnitus. Far more people experience transient tinnitus periodically in their life e.g. in stressful situation or, very common, after loud noise exposure.
A lot of research has been done to investigate the consequences of occupational or leisure time noise exposure on hearing, finding temporary threshold shifts (TTS) and not rarely tinnitus (Babisch W. 1988; Sadhra S. 2002). Transient tinnitus was reported in 66% of visitors always or nearly always after discotheque attendance, 45% of all visitors showed temporary hearing-loss (Rosanowski, Eysholdt et al. 2006). TTS were also reported in visitors of aerobic classes after lessons of 60mins (Nassar 2001).

Far less research has been done on changes in central nervous system processing caused by leisure time noise, accompanying transient tinnitus and TTS. Delayed N100s and reduced P50/P60/P200 in acoustically evoked magnetic fields (AEFs), accompanied by transient tinnitus in 65% of all visitors and TTS of 20-25dB in all subjects immediately after an 4h discotheque visit, were reported by Emmerich et al. (Emmerich, Richter et al. 2002). Changes in AEFs diminished later together with TTS. In this study evoked potentials were used as a method to study changes in central nervous system processing involved in TTS and tinnitus. Evoked data however probably only give indirect hints regarding the central nervous perturbations caused by TTS. It is more likely, that the neural correlates of tinnitus and TTS are displayed in changes of ongoing spontaneous brain activity.

Although not much is known about the origin of transient tinnitus and TTS and its accompanying processes in the human brain, it is noteworthy that most research on animal tinnitus models have been actually investigating transient (or early) tinnitus, rather than the chronic form which is usually the matter of investigation in humans. Different hypotheses involving spontaneous activity have been made about the origin of tinnitus. Increased spontaneous firing rates (SFR) as the neural correlate of tinnitus is one of two main ideas. Evidence for this idea was found in auditory nerve fibres, after high doses of salicylate were applied, and increases in SFR were found

in the auditory nerve (Evans 1981). But there are contrary results: Low doses of salicylate did not have the same effect as high doses (Stypulkowski 1990; Muller, Klinke et al. 2003) and other ototoxic drugs, like quinine (Mulheran 1999) and aminoglycoside (Kiang 1970) or even hearing loss following noise exposure (Liberman and Kiang 1978), actually *decreased* SFR in the auditory nerve fibres and still caused tinnitus. Further counter-evidence for this hypothesis results from the fact, that tinnitus often persists, even if the auditory nerve is cut (House and Brackman 1981).

On the other hand support for the SFR-hypothesis comes from the fact, that dysfunctional cochlea receptors cause changes in SFR in the central auditory system. Reduced output from the affected parts of the cochlea resulted in less inhibition (Szczepaniak and Moller 1996; Milbrandt, Holder et al. 2000) and therefore led to increased SFR in central auditory structures (Salvi 2000).
Decrease of inhibition has been demonstrated indirectly by an increase in SFR in neurons of the central and external nuclei of the inferior colliculi (Jastreboff and Sasaki 1986; Chen 1995) and an increase of SFR in the secondary auditory cortex (Eggermont 1998), following the application of low doses of salicylate.
A problematic aspect of the SFR hypothesis however is, that tinnitus sensation usually develops immediately after noise exposure, however it takes hours for SFR to increase in primary auditory cortex (Norena and Eggermont 2003) and even several days in the dorsal cochlear nucleus (Kaltenbach 2000).

Therefore, a second hypothesis explaining the origin of tinnitus might be helpful: Maybe the sensation of tinnitus does not originate from an increase of SFR in central auditory structures, but from an increase in synchronization of firing neurons in the auditory system. Support for this hypothesis comes from the finding, that immediately after noise trauma (Norena and Eggermont 2003) or application of quinine (Ochi and Eggermont 1997) an increase of synchronization was found in regions representing the affected frequencies. The increase of synchronization was thereby related to the amount of reorganization found in the cortical tonotopic representation after noise trauma (Norena and Eggermont 2003).

Synchronization is especially of importance, because it facilitates the summation of post-synaptic potentials. As a consequence, its signal is stronger and therefore favoured on higher levels of information processing (Niebur 2002). Several works (Singer 1999); (Fries P 2007) link this kind of synchronization of firing with oscillations of extracellular membrane potentials in the so-called gamma frequency range (coarsely defined as frequencies > 30 Hz). It is therefore imaginable that tinnitus results from an increase of gamma band synchronization in the auditory cortex and, because of its saliency, is more easily processed in higher stages and there wrongly interpreted as real sound. It is a great advantage, that these increases of synchronization can be measured as local field potentials (LFP) and even non-invasive with EEG and MEG, thus facilitating tinnitus research in humans.

Although tinnitus is not fully explained in animal models yet, great progress was made during the last decade. Still, there is a lack in studies investigating tinnitus in humans. Also, the lack of studies on transient tinnitus in humans, makes a direct comparison with results gained from animal research difficult.

In our laboratory, lots of effort has been made to investigate tinnitus in chronic patients by using magnetencephalography (MEG). We found, by comparing tinnitus patients to a healthy control group, differences between both groups: Spontaneous activity during rest was investigated and changes were found in alpha (8-12Hz), delta (2-4Hz) and gamma (50-60Hz) bands, revealing an decrease of alpha activity accompanying an increase in delta activity, both located in temporal – potentially auditory cortical – regions. Delta enhancement and alpha reduction correlated strongly with tinnitus-related distress. This effects could be especially localized in right temporal and left frontal areas. Localization was done by using a minimum norm estimation (Weisz, Moratti et al. 2005).

Gamma activity was significantly enhanced in tinnitus group and the lateralization of slow-wave triggered 55Hz was a good predictor for the laterality of tinnitus, being pronounced contralaterally to the tinnitus side (Weisz, Muller et al. 2007). At the same time, gamma activity was triggered by strong slow waves (< 6 Hz) in healthy control subjects in a way, that ~500ms before slow wave activity started, gamma was elevated, reaching its peak approximately at the same time as delta did. In tinnitus patients this modulation was less pronounced, indicating that in these subjects gamma activity may be a much more ongoing 'stable' phenomenon.

Until today, several studies have been made to investigate the role of gamma band activity in the human brain, revealing that gamma seems to be involved in conscious stimuli processing (Rodriguez E 1999; Melloni L., Molina C. et al. 2007). Local gamma synchronization after stimuli presentation is thereby triggering a global workspace of consciousness for the conscious evaluation of stimuli (Dehaene S 2001; Dehaene S 2006). Other studies assume, that gamma band activity is involved in feature binding (Miltner W, C. et al. 1998; Singer 1999), and maybe even underlies with its hypersynchronization phantom perception in general (Llineas, Ribary et al. 1999). It is therefore not unlikely that spatially restricted synchronous activity is involved in generating the phantom perception of tinnitus and that an increase in local gamma synchrony located in auditory brain regions is also found in subjects with transient tinnitus.

Although a lot of work has been done to investigate the neural mechanisms underlying tinnitus, no final model has been found to explain fully what tinnitus is and how it can be treated. Audiometrical research concentrated on hearing loss and transient tinnitus, sharpened our mind of how sensitive our ears are to noise exposure – in free time or in our occupational environment. Still, not much work was done to investigate the neural correlates of hearing loss and transient tinnitus.

Research done in the field of neuroscience explained us a lot about underlying processes of (transient) tinnitus, developing magnificent animal models, but still there is the need to study transient tinnitus in humans.
In the last years, our and other laboratories (Giraud, Chery-Croze et al. 1999; Melcher, Sigalovsky et al. 2000) have started to investigate neural correlates of chronic tinnitus in humans, finding first parallels to animal research. In this work, I want to go one step further, investigating for the first time the underlying neural mechanisms of transient tinnitus and its corresponding TTS.
For that, I invited rock musicians after 1-2 hours of band practice and measured their brain activity in rest with the MEG. Next to that, I assessed a wide spectrum of audiometrical data, questionnaires and interviews, to find connections between brain activity and audiometrical or behavioural data. To localize changes in brain activity I used an established frequency-domain beamforming technique called Dynamic Imaging of Coherent Sources (DICS).

2. Methods

2.1 Participants

In this study, the transient tinnitus was measured in 10 members of rock bands, who reported regularly from tinnitus after band practice. Participants were 22 to 40 years old (median 25, 9 men). All participants in this study gave their written informed consent before data acquisition and were compensated with 5€ per hour. They were recruited by flyers posted in a number of buildings, where bands had rehearsal rooms.

2.2 Procedure

Participants were measured two times: Once in the control condition and once as quickly as possible (usually 1-2 hours) after band practice (tinnitus condition). Both measurements were equalized in time and weekday to avoid effects of day time on assessed data. Measurements were separated for band 1 by 2 month, for band 2 and 3 by 2 weeks. The sequence of conditions were assigned to each band personally to ensure the balance of conditions. Finally, 6 band members started with the control- , and 4 with tinnitus condition.

In control condition participants were obliged to neglect band practice or being in environments of similar loudness for at least four days before measurement to ensure normal hearing and absence of tinnitus. In the tinnitus condition subjects did a normal band practice prior to data acquisition, with one investigator attending and measuring loudness (A-weighted) for a wide spectrum of frequencies using the Hand Held-Analyzer 2550 by Brüel&Kjær (Microphone Type 4189, Brüel&Kjær, Sound & Vibration Measurement A/S, Nærum, Dänemark). Participants then drove immediately to the MEG-laboratory where data were assessed. To ensure assessing audiometric and MEG data as fast as possible, the sequence of measurements varied for each person, resulting in a rotation of participants along all stations.

For both conditions pure tone audiogram, TEN-Test, hearing thresholds for 1000Hz dB HL were assessed for both ears. Exclusively in the tinnitus condition, tinnitus

intensity was matched using a tone of 1000Hz dB HL and tinnitus spectra were assessed for the ear on which subjects reported their tinnitus sensation or the dominant ear in case of bilateral tinnitus. More details on the audiometric procedures is given below.

2.3 Evaluation of Audiometric Data

In ten adults a wide spectrum of audiometric data were assessed in tinnitus and control condition.
Pure tone audiogram and TEN-Test were assessed binaurally for 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 kHz in dB SPL. Both audiometric procedures give complementary information. Whereas the pure tone audiogram helps identifying general hearing deficits, the TEN-Test (Threshold Equalizing Noise) is a screening tool to find dead regions on the cochlear (Moore BC. 2000), i.e. regions of the cochlea with putatively impaired inner hair-cells. Additionally hearing thresholds for 1 kHz dB HL were assessed binaurally.

In the tinnitus condition, subjects were asked to rate the loudness of their tinnitus on a tone of 1 kHz dB HL (tinnitus intensity matching). All audiometrical data were measured using a Clinical Audiometer (AC 40, DK-5610 Assens, Denmark).
To identify the spectral characteristics of the tinnitus sensation for each subject we used a procedure proposed by Norena et al. (Norena, Micheyl et al. 2002). In a first step participants were asked to adjust the loudness of 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 kHz pure tones to match their tinnitus loudness. In a second step they had to rate the likeness of these adjusted pure tones to their own individual tinnitus frequency. This approach creates spectral profiles for the tinnitus sensation (tinnitus spectrum). The test was run by in-house Matlab functions identical to those used in Weisz et al. (Weisz, Hartmann et al. 2006)

2.4 Questionnaires and Interviews

Participants were asked to answer a number of questionnaires and interviews concerning audiometric experiences, tinnitus, mental health and handedness.
To evaluate mental health subjects answered the M.I.N.I. (Sheehan DV 1998), a standardized interview based on DSM-V; handedness was assessed by using the Edinburgh Inventory(Oldfield 1971).
Tinnitus burden was quantified by administering the Tinnitus-Fragebogen (Goebel 1998), a questionnaire that measures the emotional and cognitive burden, the intrusiveness of tinnitus and somatic, sleeping and hearing problems, related to tinnitus.
To evaluate possible hyperacusis subjects filled out the Sound Hypersensitivity Questionnaire (*Geräuschüberempfindlichkeits-Fragebogen* (Nelting, Rienhoff et al. 2002).
In addition, general information about the subjects musical background, e.g. the instrument played by the participant, the length of time playing this instrument and being part of a band, the number of band practices per week and the side and frequency of tinnitus after band practice were assessed.

2.5 Recording of MEG Data

5min resting-MEG were recorded using a 148-channel whole-head-magnetometer (Magnes 2500WH, San Diego, Neuroimaging, San Diego, CA) placed in a magnetic shielded chamber (Vakuumschmelze, Hanau, Germany). Data were sampled with 2034.51 Hz and filtered online with 0.1Hz.
Participants lay comfortably in a supine position. They were instructed to focus on a cross, approximately 1.5m away on the ceiling, and to remain relaxed and awake. Instructions were presented to the white ceiling of the magnetic chamber via a mirror system, using a video beamer (JVCTM, DLA-G11E) and the presentation software Psycope X (an open-source experimental psychology software, www.psy.ck.sissa.it (Cohen J.D. 1993)).
In addition eye movements were assessed by an electro-ocolugram (EOG), heart rate via electro-cardiogram (ECG). To determine the head position in the MEG-

helmet, positions of five different index points and individual head shapes were digitized.

2.6 Data Analyses

MEG-Data were analysed with Matlab 7.5.0 (R2007b) using the Fieldtrip toolbox (http://www.ru.nl/fcdonders/fieldtrip).
Data were down sampled to 600Hz, pre-processed by visually inspecting epochs of 2 seconds each, and rejecting those with blinks or other obvious artefacts (e.g. strong muscle activity). Next, an Independent Component Analyses (ICA; using the 'runica' algorithm implemented in EEGLAB; Delorme & Makeig, J Neurosci Methods, 2004) was calculated to correct for heart-beat related artefacts (Arani AS 2007). In all subjects, the ECG activity was represented by 2-3 independent components. These components were rejected and the raw data reconstructed excluding ECG related artefacts. From all remaining trials, 90 trials per subject were randomly chosen for further analyses. This ensured that all analysed data sets had the same Signal-Noise-Ratio (SNR) for every subject and every condition. One subject had to be excluded, having blinks in every trial, so not enough trials were left for further analyses.

In the next step, a frequency-domain adaptive spatial filtering algorithm, called Dynamic Imaging of Coherent Sources (DICS) was used to identify sources of oscillatory changes (Gross J 2001; Liljeström M 2005). This method was primarily designed to find coherences between brain areas, but can also be used to localize sources of rhythmic activity.
For that, an individual structural MRI-scan is divided into a three-dimensional grid (1cm spacing), that covers the entire brain. The volume containing the grid points was fitted using a so-called multisphere approach which fits a separate sphere to each individual sensor (Huang MX 1999). This approach is a good compromise between oversimplified single-sphere models and time consuming realistic headmodeling. Since individual MRI-scans were not available, a standard scan was used.

Since obviously the brain anatomies between the subjects are not identical[1], the validity of this approach in yielding sensible results has been shown in running works by the group: In a first, a sound stimulation was given to subjects. Alpha desynchronizations following sound stimulation were correctly localized in the auditory cortex (Müller et al., in preparation; Hartmann et al., in preparation). Even desynchronization in auditory cortex could be identified *prior* to sound presentation, when a preceding visual cue indicated an upcoming auditory target (Müller et al., in preparation).
In different approach, various parameters for repetitive transcranial magnetic stimulation (rTMS) were given in the proximity of the auditory cortex. DICS using a "standard" brain approach correctly localized intervention effects to auditory cortical regions (Lorenz et al., in preparation). Analyses on basic brain connectivity also yield promising results (Schlee et al., in preparation). Last but not least a comparison of an eyes-open vs. eyes-closed measurement in one patient localized alpha differences correctly in occipito-parietal brain regions.

The adaptive spatial filter that is used in DICS is derived from the cross-spectral density matrix of the MEG-signal and the corresponding lead fields. The cross-spectral density matrix contains the cross-spectral density for all sensor combinations and is computed for all subjects and all conditions individually. Also the leadfield value was recomputed for each grid point for all subjects and conditions. So although for every subject the same volume is used, every grid has subject and condition specific spatial filters. The resulting spatial filters were applied to the 5 predefined frequencies of interest (FOI):
Alpha = 10 Hz with a smoothing of 2Hz (10/2), beta = 26/4Hz, gamma1 = 35/10Hz, gamma2 = 70/15Hz, delta = 4/2 Hz, resulting in the following frequency bands:
Alpha= 8-12Hz, beta= 22-30Hz, gamma1= 25-45Hz, gamma2= 55-85Hz and delta= 2-6Hz.
In order to derive course anatomical locations of the effects (using the Talairach Daemon; http://www.talairach.org), the structural MRI-scan used for this analyses, was normalized to a canonical brain.
Prior to calculation of differences in power between conditions, a normalization procedure was undertaken by transforming single-trial beamed power into t-values

[1]Obviously the approach is not less realistic than modelling the brain via a single-sphere.

under the assumption of zero activity. This was made for every subject and every condition. DICS was computed for the averaged difference of normalized t-values (control minus tinnitus condition).
Differences in t-values were then analysed in a non-parametric cluster-level statistic, identifying clusters of neighbouring grids with significant power changes. This method is used to correct for multiple comparisons in a within subject design (Maris E 2007).
The cluster alpha, a value used to preselect grids, that showed significant differences between both conditions, was $p<0.01$. To determine these significant grids, a simple paired t-test was calculated. Preselected grids were then further grouped to spatially coherent clusters and the cluster-level test statistic was defined as the sum of t-values for all grids in a given cluster. To test for statistical significance of the clusters, the statistic was repeated on 1000 shuffled data sets (randomly reassigning the condition sequence for subjects), and the cluster with the maximum sum was saved on each permutation. From the distribution of maximal cluster values the threshold was defined as the 95% percentile (alpha = 5% taking into account multiple comparisons).

Additionally a pearson correlation was calculated for each grid, associating the outcome of the source analysis with hearing loss and relative tinnitus intensity. Hearing loss was defined as the subtraction of hearing thresholds on 1kHz dB HL, measured at tinnitus and control condition. Tinnitus intensity was thereby measured by asking each participant to match tinnitus loudness on a tone of 1kHz dB HL. Hearing thresholds were then subtracted from tinnitus intensity, representing the relative tinnitus intensity of each participant. The same nonparametric cluster-level approach was used as above (thus accounting for multiple comparisons), with the difference that here on each permutation the order of hearing loss and tinnitus intensity data was shuffled. For both tests, the number of randomizations were 1000, the alpha for identifying significant grids was set to $p<0.01$ and the overall alpha equalled $p<0.05$.

Statistical analyses for audiometrical data and questionnaires were calculated in R, a statistic software (http://www.r-project.org). Calculated were thereby statistical tests to find profile changes in pure tone audiograms or in TEN-Test between both

conditions. Additionally, Pearson correlation tests were computed to find correlations within behavioural- (questionnaires) or audiometrical data.

3. Results

3.1 Audiometrical Data

Analysis of the subjective tinnitus data revealed that *all* subjects reported the presence of a tinnitus sensation. Five participants (50%) presented with bilateral tinnitus (two of these five subjects reported, that tinnitus was accentuated on their left side), the remaining 50% of subjects perceived a unilateral tinnitus (four left-sided). Individual tinnitus intensities were calculated by measuring the hearing threshold of each subject at 1 kHz dB HL and then subtracting this value from the tinnitus intensity matching on 1kHz dB HL, subjects had made additionally to rate the loudness of their tinnitus. This relative tinnitus intensity varied from near 0 to 12.5 dB, with an average of 7.1 dB. A relative tinnitus intensity of around 0 indicates that tinnitus loudness was low, close to the subject's hearing threshold.

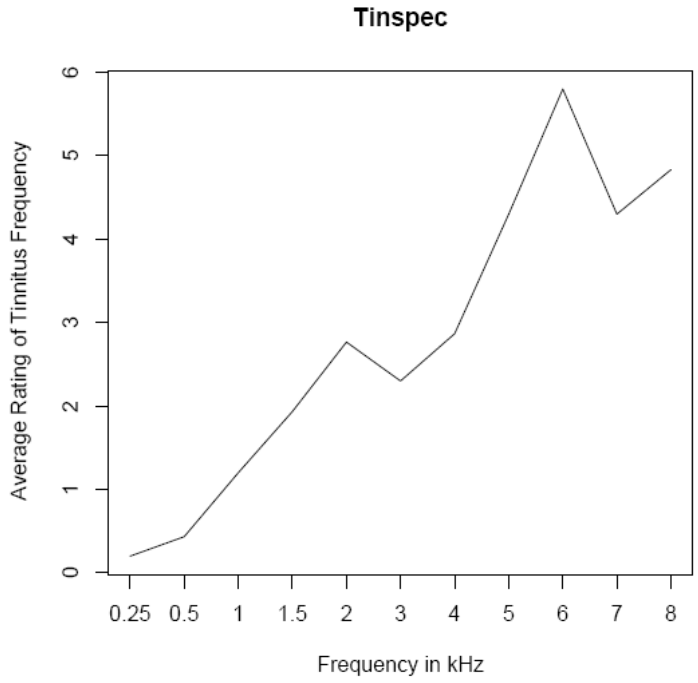

Fig.1: Averaged tinnitus spectra: Participants were asked to rate how much the sound of their tinnitus was similar to 11 frequencies, presented one by one, with each presented four times. Ratings were then averaged for each frequency within each subject and then over all subjects.

Analysis of tinnitus spectra revealed that participants rated their tinnitus on average as being most intense for higher frequencies, with a maximum around 6 kHz (Fig.1).

Measurements of sound exposure during playing of the music were made for the whole time of musical practice. The hand-held analyser was thereby placed in the middle of the very small rooms used for band practice, with the microphone turned towards the ceiling. The results differed for the three pop groups. The maximum value (dB(A)) that was achieved by each group during musical practice was 119.3 dB for Group A, 96 dB for Group B and 94.2 dB for Group C (mean across groups = 105 dB). The average loudness (LAeq) was 83 dB, 87 dB and 110 dB (mean = 95 dB).

Pure tone audiograms of both ears were analysed in R. ANOVAs with the factor condition (sound exposure vs control) were calculated separately for each ear. For the left ear a significant main effect of $F_{1,9} = 20.18$ ($p=0.001$) was found, indicating higher hearing thresholds in response to the sound exposure. The right ear showed such an effect, if tested one-tailed $F_{1,9}=3.58$ ($p<.05$, one-tailed).
Paired t-test were calculated separately for each frequency, averaging hearing thresholds of all subjects for each frequency in tinnitus and control condition, revealing significant differences for 1 kHz ($p=0.02$, $t=2.89$), 5 kHz ($p=0.03$, $t=2.63$) and 6 kHz ($p=0.04$, $t=2.37$) in the left ear (Fig.2), and 3 kHz ($p=0.001$, $t=4.54$) in the right ear (Fig.3).
Hearing loss in the right ear was more prevalent in higher frequencies, suggesting that the right ear is more sensitive to hearing loss in higher frequencies, whereas the left ear, showing a stronger and more equally distributed hearing loss, is more sensitive to hearing loss in general.

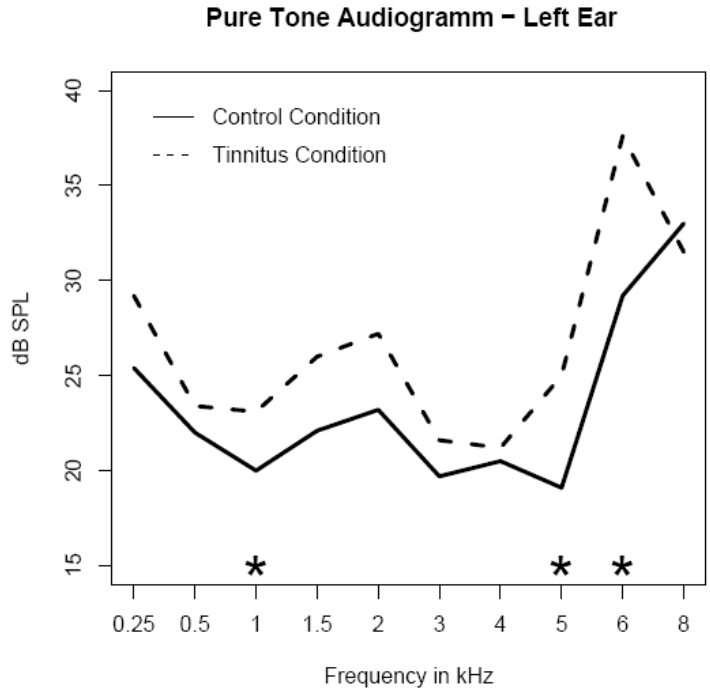

Fig.2: Pure tone audiogram of the left ear averaged across all subjects. Note that higher values in dB SPL means higher hearing thresholds, which corresponds to greater hearing loss. Significant differences between conditions were found at 1, 5 and 6 kHz.

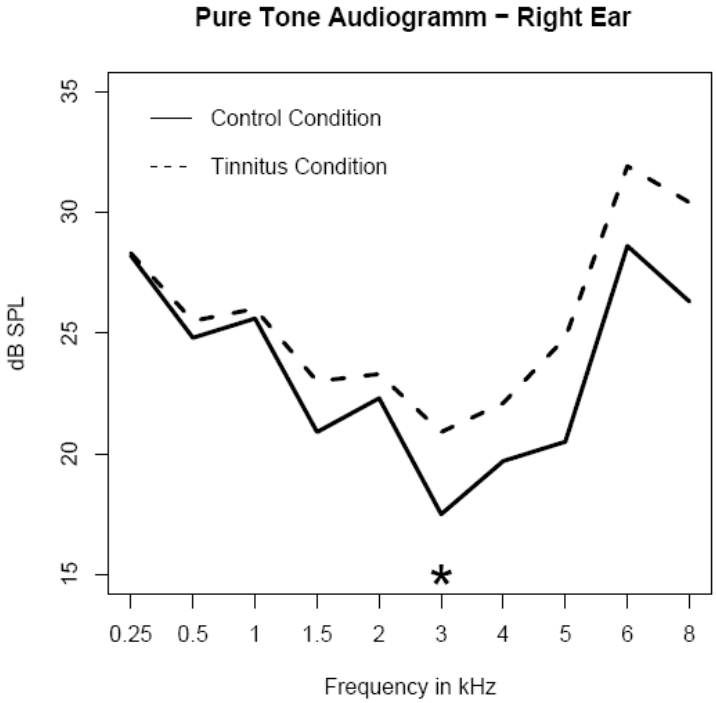

Fig.3: Pure tone audiogram of the right ear averaged across all subjects. Note that higher values in dB SPL mean higher hearing thresholds, which corresponds to the amount of hearing loss. Significant differences between conditions were found at 3 kHz.

The results of the TEN-test did not show a significant change of dead regions after noise exposure compared to the control condition. This was calculated with a paired t-test. A further analysis was made to ensure these finding: A paired-t test was calculated for each frequency, comparing the over all subjects averaged hearing level for both conditions. There was no significant outcome for the right ear ($p>0.23$, $t> -1.74$), only for the left ear, a significantly increased threshold was found at 4 kHz ($p=0.02$, $t=-2.7$).

Additionally a Pearson product-moment correlation was calculated for the average hearing loss of different frequencies and the ratings of analogous frequencies in the averaged tinnitus spectrum. A significant correlation was found for the right ear with $r= -0.83$ ($p=0.003$, $t=-4.18$), see Fig.4. This means that frequencies at which hearing loss was pronounced, were more likely to be rated as being part of the tinnitus spectrum. There was no significant effect found for the left ear ($p=0.44$, $t=-0.81$).

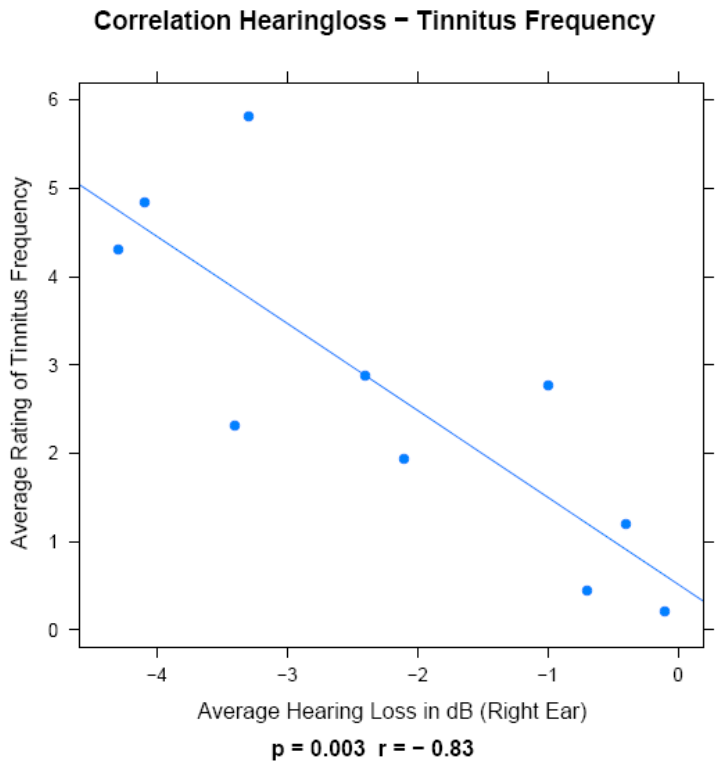

Fig.4: A pearson correlation was calculated for 10 frequencies (0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 kHz): It was thereby the average right ear hearing loss per frequency (hearing threshold (control condition) minus hearing threshold (tinnitus condition)) correlated with the average tinnitus rating of each frequency.

3.2. Questionnaires

Analysis of questionnaires revealed that participants varied in their musical experience: The average length of total instrumental practice was 14.1 years (6-23 years). Participants played in rock bands – with comparable loudness as reported in this study - for 6.3 years on average (1-22 years, median = 4.5 years). Participants practiced 3-6 hours per week.

Scores on the Tinnitus Questionnaire (Goebel 1998) ranged from 3 to 27 out of 84 points (median = 6.5). Scores can therefore be interpreted in a way that participants did not feel much burdened by their tinnitus. Hyperacusis was assessed by the *Geräuschüberempfindlichkeits*-Fragebogen (Nelting, Rienhoff et al. 2002). Also here, scores indicated low degrees of hyperacusis, varying from 0-15 out of 45 points (median = 4).

A pearson correlation calculated for the hyperacusis score and the total amount of years since inception of musical practice, revealed a positive relation of r=0.63 (p=0.05, t=2.28) (Fig.5).

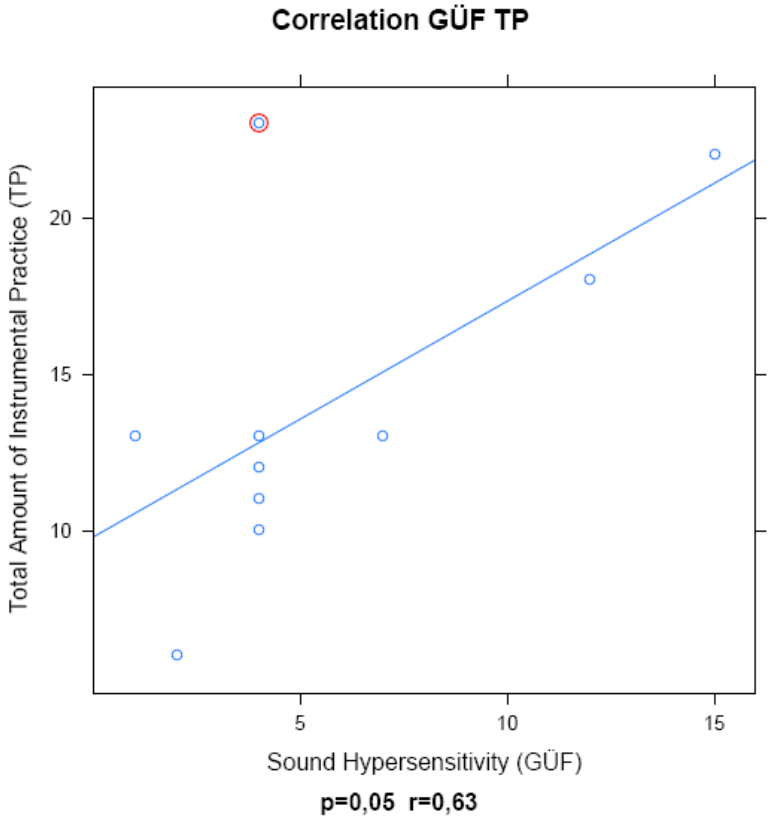

Fig.5: The total amount of instrumental practice (TP) (in years) participants reported and the hyperacusis test values (GüF) were calculated in a pearson correlation, revealing that the longer participants played their instruments, the more they became sensitive to sounds. Note that the double circle labels a female participant.

3.3 Neuromagnetic Data

3.3.1 Source Analysis

In order to map neural oscillatory responding to serious sound exposure and musical performance in comparison to the control condition, DICS was calculated for 5 frequencies of interest (FOI): delta= 2-6Hz, alpha= 8-12Hz, beta= 22-30Hz, gamma1= 25-45Hz, and gamma2= 55-85Hz. The auditory cortex was defined as the region of interest (ROI).

Negative power changes were found for the gamma2 band in the superior temporal lobe, with the maximum change located in BA 22 (Fig.6). This means that exposure to loud music during practice resulted in enhanced gamma2 activity in regions of the auditory cortex. Although this effect was only a trend on the relatively conservative cluster level ($p=0.1$), there was a strong effect for several dipoles ($p<0.01$). Lying in the pre-defined ROI and the difference being in the hypothesized direction, it should be therefore reported as an important result, especially if it is taken into account, that the sample size was low. A look at the individual data showed that *all* participants increased gamma2 in this region in response to the exposure.

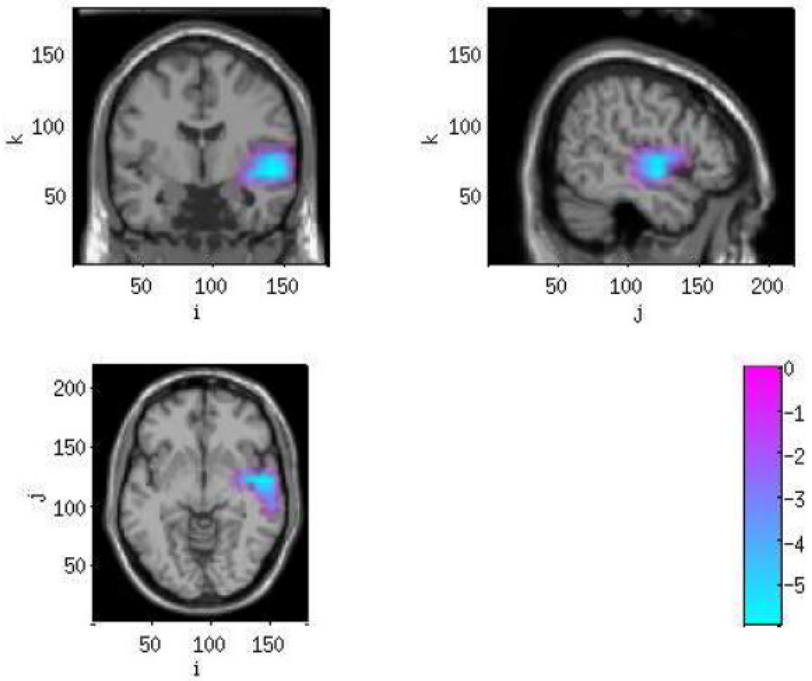

Fig.6: Increased power in gamma2 were found in the superior temporal lope, centred in BA 22, auditory cortex following band practice. This change was a trend on cluster level ($p=0.1$). Lying in the ROI, this cluster is still important to be reported, revealing, that relative short stays (1-2 hours) in very loud environments can cause temporary gamma2 increases in auditory cortex. Changes are displayed in t-values.

Analysis of the other FOIs revealed significant power increases on cluster level in the tinnitus condition for alpha, slow waves and gamma1. All power changes were thereby centred in the precuneus (BA7).

This means, that high sound levels cause temporary increases in alpha-, slow wave- and gamma1 bands, that centre in the precuneus (BA7). Fig.7 shows power changes exemplary for the slow wave band (2-6Hz), see figures of power changes in alpha and gamma1 in the appendix (Fig.1 and 2).

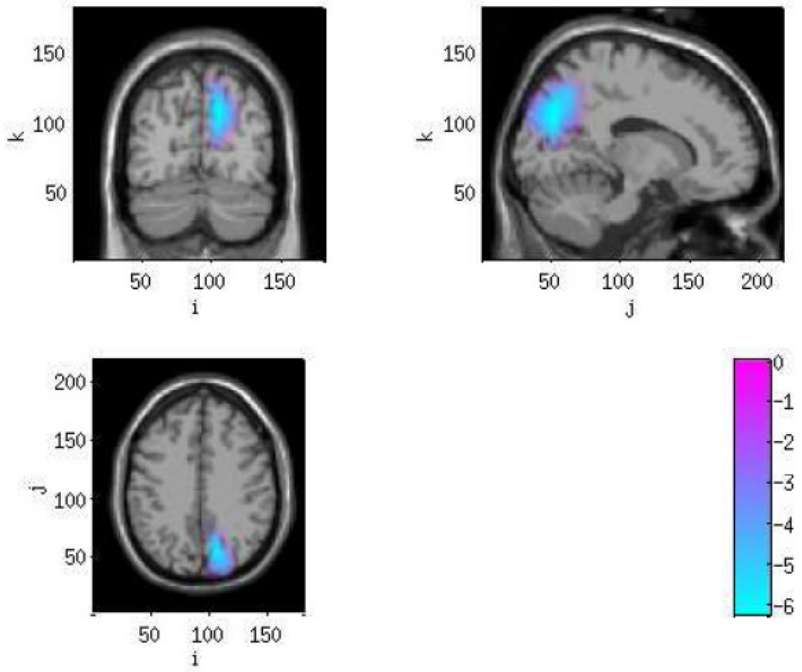

Fig.7: Power increase in tinnitus condition found in the precuneus (BA7) exemplarily shown for slow waves. Power changes were calculated on cluster level with $p<0.05$ and grid level $p<0.01$ and are displayed in t-values.

There were no changes in power found in the beta band.

3.3.2 Source Correlation

Results of Pearson product-moment correlations for the outcome of source analyses with hearing loss and relative tinnitus intensity on cluster level showed no significant effects for the auditory cortex. Instead there were significant correlations found in the alpha-, gamma1- and slow wave band in other brain regions.

For the alpha band, the relative tinnitus intensity correlated perfectly ($r= 0.95$) with a cluster lying in the left medial frontal lobe having its centre in BA10. This means, that

the less alpha activity was found in the medial frontal lobe after the exposure (=post), the stronger was the transient tinnitus at that time. See Fig.8 for the localization of the correlation of alpha activity and the relative tinnitus intensity and Fig.9 for the corresponding scatter plot.

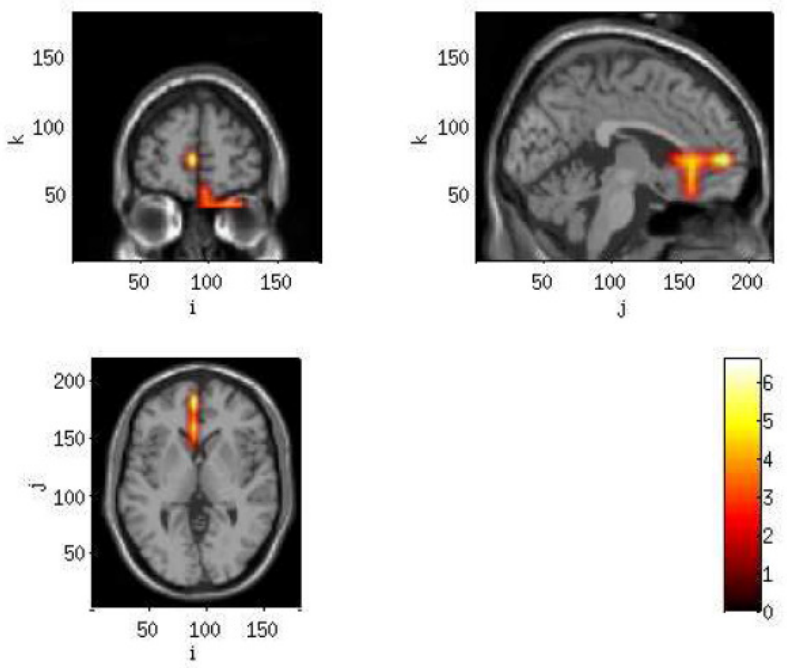

Fig.8: Alpha band activity correlated highly with relative tinnitus intensity (r=0.95), having its centre in the left medial frontal lobe (BA10). Cluster alpha was p<0.01, overall alpha p<0.05. Correlation strength is displayed in t-values.

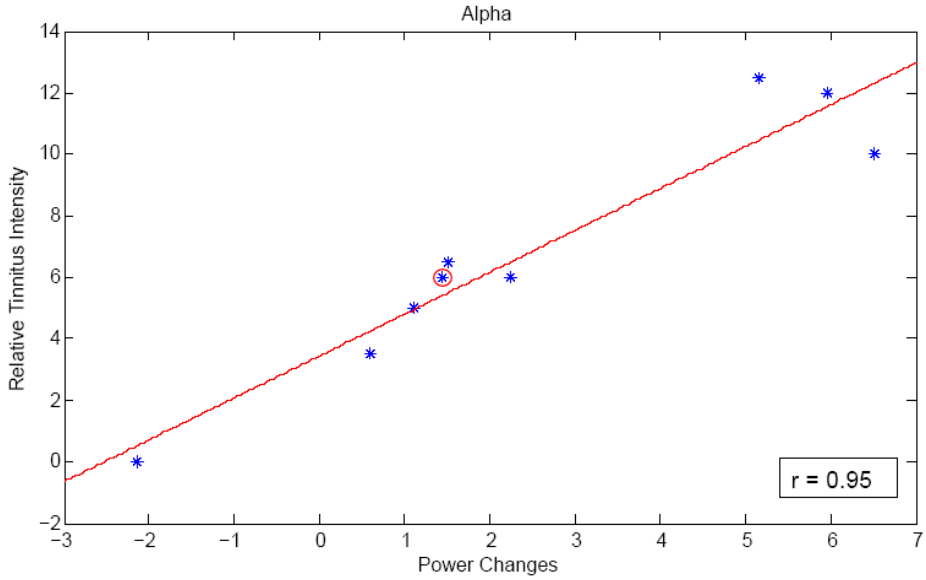

Fig.9: This scatter plot shows the correlation of alpha band activity and relative tinnitus intensity. The less alpha activity was found in the medial frontal lobe in tinnitus condition (=post), the stronger was the transient tinnitus after band practice. Note that the circle labels a female participant.

In the gamma1 band a positive correlation of r= 0.95 was found for the relative tinnitus intensity and the posterior cingulum, with the maximum centred in BA 30, meaning that the less gamma1 activity is found in the posterior cingulum in tinnitus condition, the stronger is the tinnitus perception after band practice (Fig. 10 and 11 show the significant cluster and the corresponding scatter plot for this correlation.

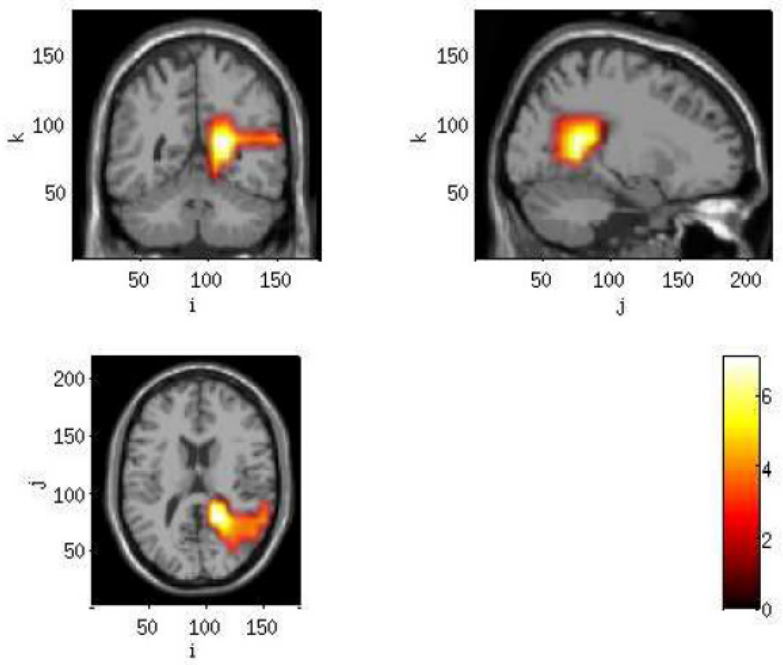

Fig. 10: Pearson correlation on cluster level revealed significant effects for the relative tinnitus intensity and right posterior cingulum, with its maximum centred in BA30 and a correlation of r= 0.95 (displayed in t-values). This effect indicates, that the less gamma1 activity is present in the right posterior cingulum after noise exposure, the stronger is the tinnitus perception.

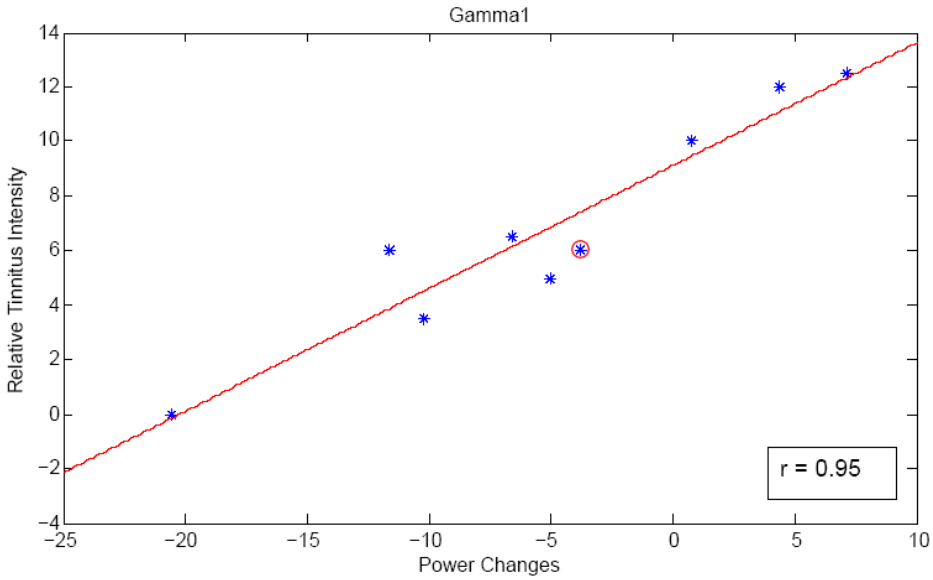

Fig. 11 : The scatter plot of the relative tinnitus intensity – source level correlation for the right posterior cingulum ensures, that significance was not obtained by outliers. Cluster alpha was thereby p<0.01, overall alpha was p<0.05. Note that the circle labels the female participant.

For slow waves a negative correlation of r= -0.91 was found for hearing loss and source data of the hippocampal gyrus and the amygdala of the right hemisphere. This means, the less alpha activity was found in these regions in tinnitus condition, the greater hearing loss was after band practice (Fig. 3 and 4 in the appendix show the significant cluster and the related scatter plot).

A negative correlation in the alpha band was found for hearing loss and the right anterior cingulum, centred in BA24 with r = -0.95. A negative correlation coefficient for a prepost (source analyses data)- prepost (hearing loss) correlation means, that the less alpha is found in the right anterior cingulum in tinnitus condition, the higher is the hearing threshold after band practice, which equals worse hearing.
Fig.5 in the appendix show the significant cluster in BA24 obtained by cluster correlation with cluster alpha of $p<0.01$ and an overall alpha of $p<0.05$. Fig.6 in the appendix shows its corresponding scatter plot.

5.Discussion

To my knowledge, this study is the first one to investigate spontaneous activity changes in ongoing brain behaviour following transient tinnitus and its accompanying temporary hearing loss in humans. Next to the assessment of audiometrical and cerebric data, I used a frequency domain beamforming technique called Dynamic Imaging of Coherent Sources (DICS) to localize changes in central nervous system processing (Gross J 2001) and to correlate them with the assessed audiometrical data.
Analysis of audiometrical data revealed temporary threshold shifts (TTS) in both ears, although more pronounced in the left ear. Threshold enhancements were distributed across the entire hearing spectrum (measured here between 0.25-8 kHz). For the right ear, hearing-loss was stronger for the higher frequencies. For both ears – on average - no dead regions were found, although participants showed temporary hearing loss.

A very important finding in this study is, that analysis of tinnitus spectra revealed that participants rated their tinnitus on average highest for upper frequencies, with a maximum in 6 kHz and that this correlated positively to the amount of average hearing loss. This means that those frequencies in which hearing loss was pronounced, were more likely to be rated belonging to the tinnitus spectrum. Similar effects were found in studies investigating chronic tinnitus (Norena, Micheyl et al. 2002), bringing further support to the hypothesis, that hearing loss is basic for the generation of tinnitus even on a short time-scale.

Emmerich et al. (2002) hypothesized that early occurrence of tinnitus accompanied by TTS could be due to damage in outer hair cells. Support for this idea comes from experiments, that found degenerative processes in single outer hair cells in guinea pigs, after noise exposure (Emmerich, Richter et al. 2000; Linss, Linss et al. 2000) and from the fact, that the accumulation of these micro injuries was reflected in the increase of transient tinnitus in adults aged 20-24 years, visiting discotheques on a regular basis (Emmerich, Richter et al. 2002).
In this group also an increase of persistent threshold changes (PTS) was observed. It should be noted, that there is counter evidence for an increase of PTS (Axelsson, Eliasson et al. 1995). No increase of hearing thresholds within 16 years was found in rock/pop musicians. Only 13% of all participants had an hearing loss >20 dB at a high frequency pure tone average (3, 4, 6 and 8kHz), when they were tested 16 years after the first examination.

The other important finding of this study was that high gamma oscillations (gamma2; 55-85 Hz) increased in the right auditory cortex when tinnitus was existent. It is thereby not known if increases in high gamma are due to hearing loss, transient tinnitus or both, because non of both correlated significantly with power changes in gamma2 in auditory cortex.
This does not mean, that hearing loss and tinnitus are not related to the increase in high gamma, but that no linear relationship exists. Also it has to be kept in mind that hearing loss and tinnitus intensity were very moderate, yielding a low variability for the calculation of linear correlations. Also, the cluster-level statistic accounting for multiple comparisons can be seen as rather conservative, which can be seen at the very high correlation values needed to yield a significant cluster ($r > .9$).

In order to test whether the right auditory cortical gamma2 increase was related to the higher left-ear hearing-loss I repeated the correlation test specifically for the right auditory cortical cluster (Fig.6).
A correlation of r = 0.44, that was not significant, was found. It is apparent, that there is a weak trend for a relationship between hearing loss in the left ear and the increase in high gamma in the right auditory cortex. To ascertain these result, one would have to enlarge sample size or test in an additional study, if subjects with TTS but without tinnitus show similar results in source analyses. If yes, increase in gamma2 would be due to hearing loss.

It is thereby of importance to emphasize that high gamma activity increased for every single subject in tinnitus condition. To ensure this, we tested this finding for all subjects, by extracting all grids that were parts of the right auditory cluster for each subjects and averaged them. Averaged values were then tested against zero, revealing that gamma increase in tinnitus condition was highly significant ($p = 0.0001$, $t = -6.81$).
The finding, that high gamma increases in auditory cortex when transient tinnitus and TTS are existent, conforms to the gamma increase found in chronic tinnitus in humans (Weisz, Muller et al. 2007), and could be related to increases of SFR or synchronized firing in secondary auditory cortex following the application of low doses of salicylate or noise (Eggermont 1998; Norena and Eggermont 2003).

Based on other animal studies regarding gamma and synchronized firing (Singer 1999; Fries P 2007), as well as its implication in perception and higher cognitive functions (Womelsdorf T 2006; Fries P 2008; Zeitler M 2008) it is tempting to hypothesize that the increased high gamma found in the present study accompanies synchronized firing in the auditory cortex. Unfortunately, there is no animal study so far that relates these findings on action potentials with LFPs which would help to resolve this issue.
The increase in gamma band activity, its supposed relationship to hearing loss and the fact, that tinnitus frequencies correlated positively with hearing loss (see above), gives therefore further support for the hypotheses that tinnitus is caused by an deafferentation of auditory structures, which is followed by hyperactivity and an increase of synchronization in the auditory cortex.

It is important to note, that in this study no decrease of alpha activity in the auditory cortex was found, contradicting the hypotheses, that inhibitional processes are necessary for an increase in synchronization in auditory cortex and for the perception of tinnitus, because alpha activity is hypothesized to be strongly associated with inhibitional processes (Miller 2006).

Because of using DICS, a technique that enabled us to look for power changes all over the brain, we found in three of our 5 frequencies of interest (alpha, gamma1 and slow wave) significant power increases in tinnitus condition in the precuneus, an area located in the medial part of the posterior parietal lobe. This area is an highly integrative structure, supposed to be involved in visuo-spatial imagery, episodic memory, self-consciousness - and the shifting of attention (Le TH 1998).
Several studies agree, that the precuneus is activated when attention needs to be shifted between object characteristics (Fink GR 1997; Nagahama Y and al. 1999), or between two different tasks (Culham JC 1998). Further research needs to be done, to study involvement of the precuneus in conscious perception of tinnitus, but it is not unlikely that the precuneus plays an active role in shifting attention to the transient tinnitus sensation.
In chronic tinnitus patients nothing is known about power changes in the precuneus compared to a healthy control group. This is probably due to the fact, that in chronic tinnitus patients, the tinnitus sensation is not a new, but an always existent stimuli. In patients, who suffer strongly from tinnitus, attention is always fixed to the tinnitus sensation. Therefore a conscious shift might not be necessary. Chronic tinnitus patients, that do not suffer from tinnitus, stopped paying attention to tinnitus, and therefore are not constantly shifting attention willingly to it.

Additionally, we found, that the relative tinnitus intensity correlated highly with a decrease of alpha band activity in left prefrontal structures. Alpha is hypothesized to be involved in inhibitional processes in the brain (Miller 2006). Less alpha activity in prefrontal structures in tinnitus condition could be therefore an indicator of a general increased activation of these regions. There are several evidences for an prefrontal involvement in tinnitus (Mirz, Pedersen et al. 1999; Mirz, Gjedde et al. 2000). In our laboratroy, we found, that tinnitus distress correlated positively with an increase of delta activity and a decrease of alpha activity in the left prefrontal cortex (PFC)

(Weisz, Moratti et al. 2005). Aditionally, Jastreboff described the PFC as a “candidate for the integration of sensory and emotional aspects of tinnitus”(Jastreboff 1990).
If the relative tinnitus intensity is positively correlated to alpha decrease in the PFC, it is not unlikely that this structure is involved in the conscious perception of transient tinnitus.

Furthermore hearing loss was negatively correlated to alpha reduction in BA 24, a structure that is part of the anterior cingulum (ACC), which is known to be involved in error detection (Ladouceur CD 2007; Burle B, Roger C et al. 2008). To understand how this structure is involved in tinnitus, further research is needed.
Additionally hearing loss correlated with decreased slow wave activity in the amygdala and the parahippocampal gyrus. The less slow wave activity was found in the amygdalohippocampal complex, the stronger was the hearing loss pronounced.
Although some studies reported involvement of the amygdala and the parahippocampal gyrus in the sensation of tinnitus, suggesting e.g. involvement of both structures in the establishment of an auditory memory for tinnitus (Shulman 1995), it is not possible at this stage to interpret these finding. Further research will be needed.

One last correlation was found for the relative tinnitus intensity and gamma1 activity in the right posterior cingulum: The higher the gamma decrease in tinnitus condition in BA30, the stronger tinnitus was perceived. The posterior cingulum is hypothesized to be part of the neural network correlates of consciousness (NNCC), that also involves the precuneus (Vogt BA 2005). Additionally, it is involved in the emotional colouring of perception and pain processing (Bromm 2001; Benuzzi F 2008; Park JY 2008).
It is therefore not unlikely, that the posterior cingulum is engaged in the conscious processing of the tinnitus sensation, especially in the evaluation of the emotional impact of the tinnitus perception.

It is astounding to see, how short stays in loud environments can trigger global changes in brain activity. Having in mind, that repeated exposure to noise can cause an accumulation of micro injuries to outer hair cells in the cochlea and therefore increase the transient tinnitus rate (Emmerich, Richter et al. 2000; Linss, Linss et al.

2000; Emmerich, Richter et al. 2002) it is not unlikely that repeated noise exposure is an elicitor for enduring global changes in central processing, that facilitates the development of chronic tinnitus.
Another indicator for the increased sensitivity of the auditory system caused by repeated exposure to high sound levels is our finding that hyperacusis level increased with the total amount of years, band members practiced their instruments.

Adding all findings together, one could hypothesize a model that explains how transient tinnitus changes to chronic tinnitus. Temporary hearing loss causes transient tinnitus, that is consciously evaluated by the PFC and the posterior cingulum. With an increasing number of micro injuries in outer hair cells, the rate of transient tinnitus increases as well, which is noticed by the PFC and negatively evaluated by the posterior cingulum. The precuneus is therefore shifting attention to the tinnitus sensation each time it occurs, which enhances stimuli processing (Moran J 1985) in the auditory cortex and is thereby eventually facilitating enduring global changes in central processing, leading finally to the development of chronic tinnitus.

Very important in this model could be also the emotional state in which tinnitus occurs. If transient tinnitus follows exposure to loud environments, which are evaluated negatively (e.g. a 5th grade teacher, who hates screaming children and his job in general, and who has tinnitus after a stressful day, which is making him even more angry), the person's emotional state can further aggravate the negative evaluation of tinnitus and thus amplifying effects of attention and emotion on stimuli processing, facilitating therefore the development of chronic tinnitus even more.

To further investigate this idea, it would be necessary to calculate e.g. a phase-locking analyses (Lacheaux, Rodriguez et al. 1999), that uses the phase difference between two recorded signals to see if the phase difference is constant over time. Using this analyses one would be able to see, if those brain areas hypothesized to form a network that establishes the conscious perception of transient tinnitus, are phase-locked to each other.

The fact that we found no alpha decrease in the auditory cortex in subjects with transient tinnitus, may lead to the conclusion, that alpha decrease is not a necessary requirement for the perception of tinnitus. It could be therefore hypothesized, that the decrease of alpha activity increases over time as an indicator for the transition from transient to chronic tinnitus, reflecting the increase of enduring changes in central processing.

Seeing the global changes in central processing due to noise exposure it is of fundamental importance, to protect the auditory system during noise exposure by using hearing protections aids. Unfortunately, acceptance of hearing protection devices is low. This is due to the fact, that e.g. sound quality of music decreases, when hearing protection is used (Mendes, Morata et al. 2007).
In addition most people underestimated the likeliness of hearing loss due to loud music. Especially young people believed, that they would not suffer from hearing loss until greater age. Although 66% of them reported having experienced tinnitus in their lives, only 42% were concerned about it (Rawool and Colligon-Wayne 2008).
It is therefore important to 1.) inform especially young people about their risks to develop hearing loss and tinnitus due to noise exposure, and 2.) to develop better hearing protection devices that are not expensive and comfortable to use. Maybe by that, one can prevent that more and more people develop hearing loss and chronic tinnitus due to leisure-time and occupational noise.

5. Literature

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6. Appendix

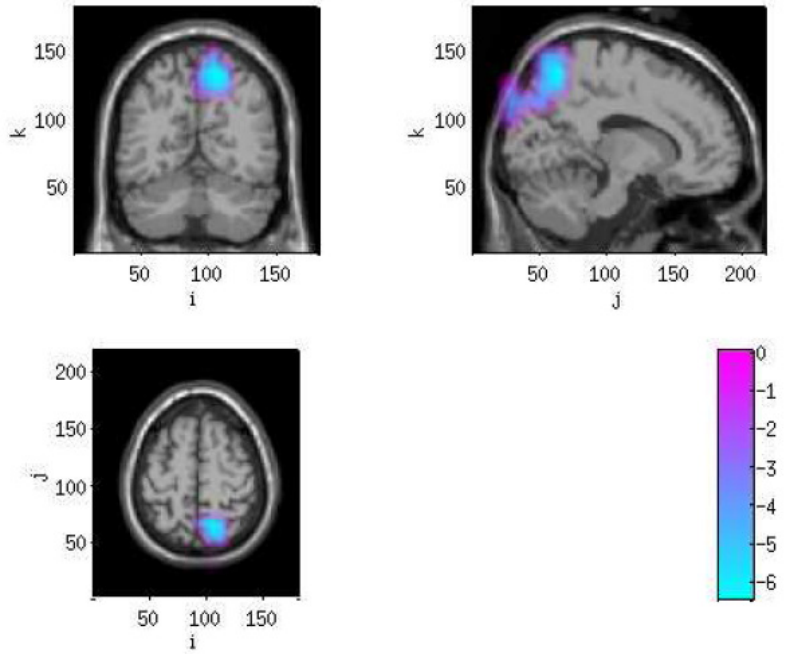

Fig.1: : Power increase in tinnitus condition found in the precuneus (BA7) shown for alpha. Power changes were calculated on cluster level with p<0.05 and grid level p<0.01 and are displayed in t-values.

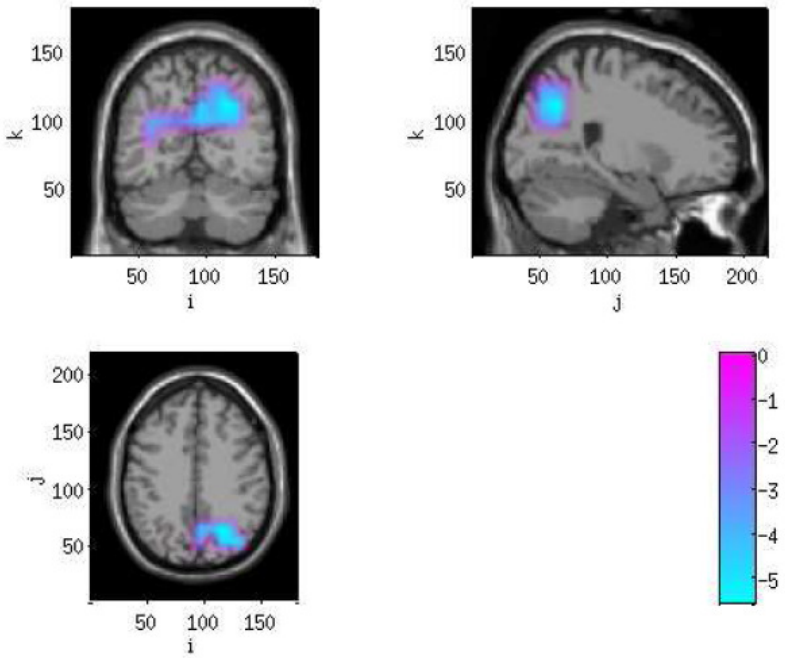

Fig.2: : Power increase in tinnitus condition found in the precuneus (BA7) shown for gamma1. Power changes were calculated on cluster level with p<0.05 and grid level p<0.01 and are displayed in t-values.

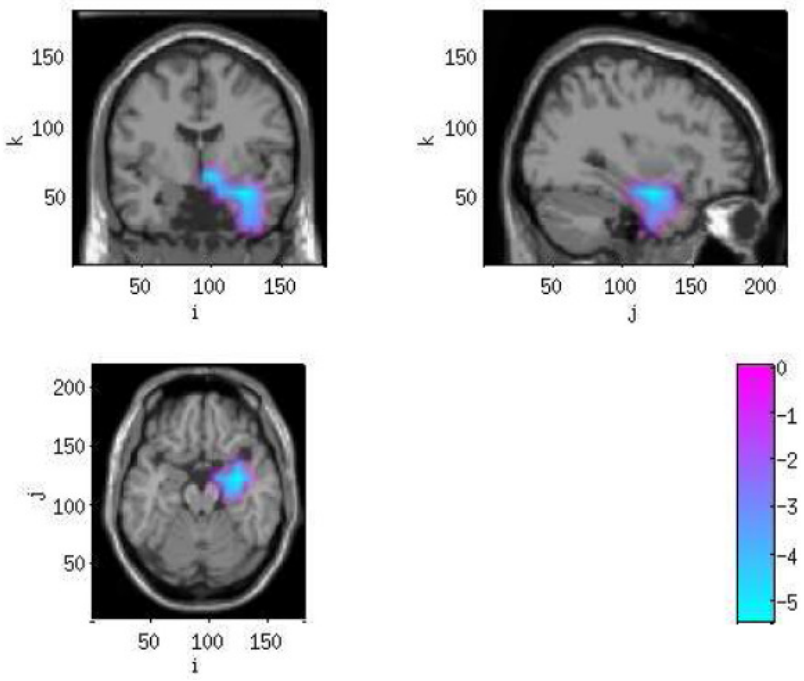

Fig. 3: Pearson correlation on cluster level for the slow wave band revealed significant effects for hearing loss and right amygdalohippocampal complex with a correlation of r= -0.91 (displayed in t-values). This effect indicates, that the less slow wave activity is present in the amygdalohippocampal complex after noise exposure, the stronger is the hearing loss.

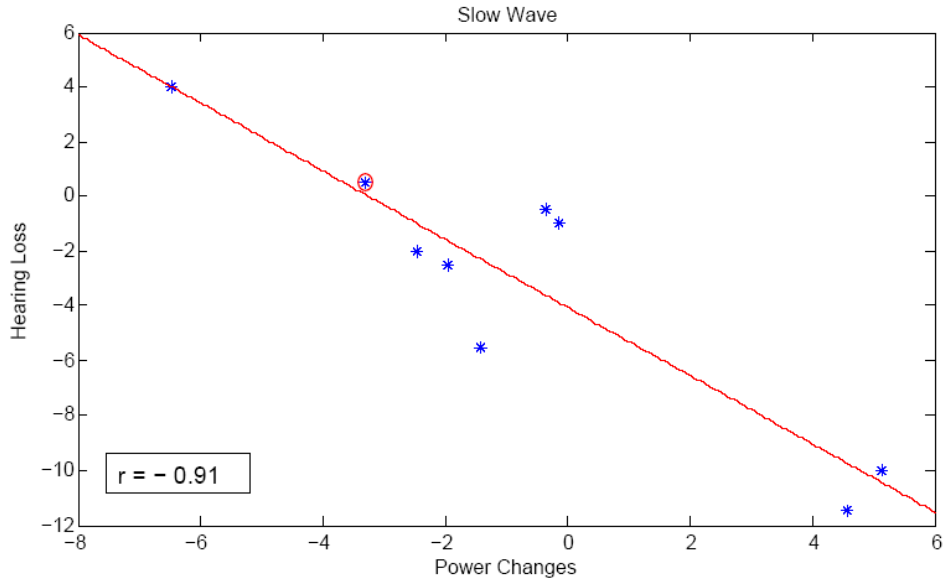

Fig.4: The scatter plot of the hearing loss – source level correlation for the right amygdalohippocampal complex ensures, that significance was not obtained by outliers. Cluster alpha was thereby p<0.01, overall alpha was p<0.05. Note that the circle labels a female participant.

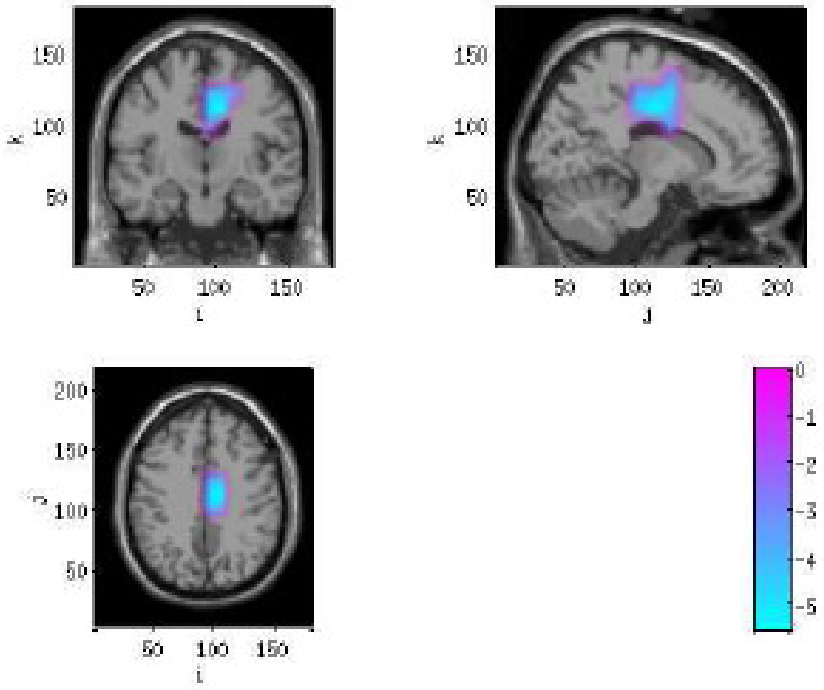

Fig.5: Pearson correlation on cluster level for the alpha band revealed significant effects for hearing loss and the right anterior cingular cortex with its maximum centred in BA 24 and r= -0.95. This effect indicates, that the less alpha activity is present in the cingulum after noise exposure, the stronger is the hearing loss. The cluster is scaled in t-values.

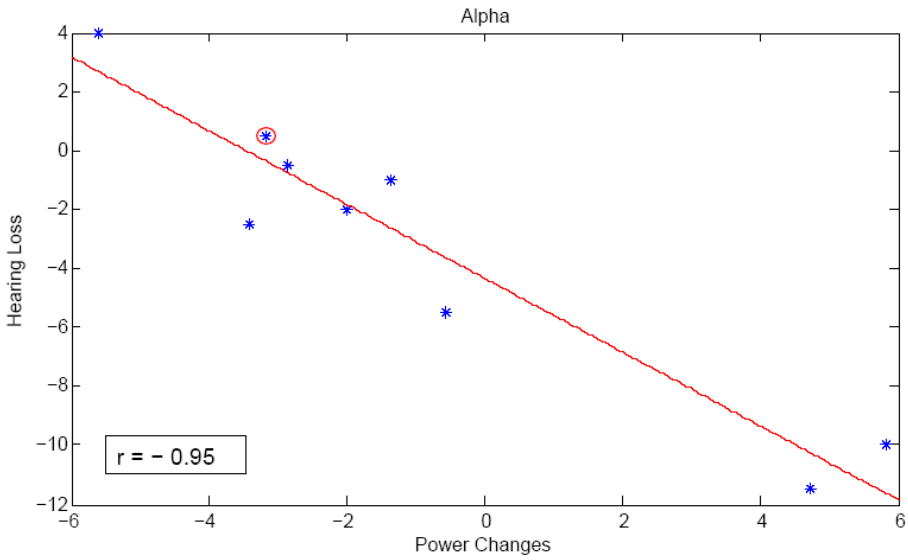

Fig.6: The scatter plot of the hearing loss – source level correlation for the right anterior cingulum ensures, that significance was not obtained by outliers. Cluster alpha was thereby $p<0.01$, overall alpha was $p<0.05$. Note that the circle labels a female participant.