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Positron emission tomography of cortical centers of tinnitus

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Abstract

Tinnitus is associated with a wide variety of disorders in the auditory system. Whether generated peripherally or centrally, tinnitus is believed to be associated with activity in specific cortical regions. The present study tested the hypothesis that these cortical centers subserve the generation, perception and processing of the tinnitus stimulus and that these processes are suppressed by lidocaine and masking. Positron emission tomography was used to map the tinnitus-specific central activity. By subtracting positron emission tomography images of regional cerebral blood flow distribution obtained during suppression of the tinnitus from positron emission tomography images obtained during the habitual tinnitus sensation, we were able to identify brain areas concerned with the cerebral representation of tinnitus. Increased neuronal activity caused by tinnitus occurred predominantly in the right hemisphere with significant foci in the middle frontal and middle temporal gyri, in addition to lateral and mesial posterior sites. The results are consistent with the hypothesis that the sensation of tinnitus is associated with activity in cortical regions functionally linked to subserve attention, emotion and memory. For the first time, the functional anatomy of conditions with and without the habitual tinnitus sensation was obtained and compared in the same subjects.

Key words: Tinnitus; Positron emission tomography; Functional brain imaging

1. Introduction

Tinnitus is a frequent and often devastating symptom of disorders of the auditory system and a wide variety of other pathological conditions (Lechtenberg and Shulman, 1984; Seidman and Jacobson, 1996; Coles, 1997). The lack of an evident external sound stimulus associated with the experience of tinnitus has led to the definition of tinnitus as an auditory 'phantom' perception (Jastreboff, 1990). Many dysfunctions of the auditory system, resulting in aberrant neural activity, have been proposed as the cause of tinnitus (Jastreboff, 1990), yet no theory of the underlying pathophysiology has been substantiated. Most hypotheses claim that tinnitus is related to cochlear dysfunction (Coles, 1997). Damage to hair cells due to noise or ototoxic drugs, stereocilia decoupling, changes in calcium ion concentration or disturbance of the synaptic transmission were suggested most frequently as possible cochlear causes (Romand, 1992; Zenner and Ernst, 1993; Lenarz et al., 1995; Lepage, 1995). Pathologic changes in the acoustic nerve with cross-talk between adjacent fibers as a result of insufficient insulation (due, for example, to retro cochlear pathology) (Møller, 1984) or imbalance between the activity of large fibers innervating the outer hair cells and small inner hair cell fibers are other possible patho-mechanisms (Tonndorf, 1987; Møller, 1997). Additionally, abnormal activity at higher levels of the auditory pathways (auditory nuclei, auditory cortex, associative cortices) may contribute to the generation of tinnitus (Jastreboff et al., 1988; Meikle, 1995; Gerken, 1996; Jastreboff, 1996a). Despite this profusion of assumed locations of the generator of tinnitus, most current hypotheses agree that abnormal neural activity

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is interpreted and perceived as tinnitus in higher cortical centers (e.g. auditory cortex) (Jastreboff, 1990).

The interpretation of an aberrant auditory signal as 'troublesome tinnitus' not only implies a process of conscious sound processing in auditory centers, but must at the same time associate the signal with unpleasantness and distress. Memory, attention and the emotional state of the patients are factors supposed to be involved in this reaction. Thus, an evaluation of the cerebral function in tinnitus sufferers may uncover the underlying neurophysiological process.

The only clinically available measure of tinnitus is the psycho-acoustical description of pitch and loudness, which is based on a subjective match between tinnitus and external sounds (Goldstein and Shulman, 1981; Coles et al., 1984; Hallam et al., 1985). A satisfying match is often impossible. In other cases, it is unsatisfactory due to temporal fluctuations and poorly reproducible measurements. The match to the audiologic features gives some information about the characteristics of the sensation, but does not allow for predictions of the treatment outcome, or severity, or the degree of annoyance and dislike involved (Hazell et al., 1985; Jastreboff et al., 1994). Without useful objective measurements, confirmation and validation of tinnitus for medico legal purposes is impossible.

In an attempt to demonstrate objective evidence of tinnitus, a link to the presence of spontaneous otoacoustic emissions (SOAE) and tinnitus was suggested, but appeared to be weak (Wilson, 1986; Penner and Burns, 1987; Penner, 1990; Ceranic et al., 1995). Compared to controls with normal hearing, brainstem auditory-evoked responses in patients with tinnitus showed consistently significant differences (Shulman and Seitz, 1981; Ikner and Hassen, 1990; Lemaire and Beutter, 1995; Attias et al., 1996). Unfortunately, these differences could not be reproduced in other studies (Barnea et al., 1990; Møller et al., 1992). Conflicting results were also found in experiments using magneto-encephalography. Some studies reported that auditory-evoked magnetic fields in tinnitus sufferers were different from those of normally hearing individuals (Hoke et al., 1989; Pantev et al., 1989; Shiomi et al., 1997). Others failed to replicate these results (Jacobson et al., 1991; Colding-Jørgensen et al., 1992).

With the development of functional brain imaging techniques, such as single photon emission-computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), new potential methods for the objective measurement of tinnitus have emerged. These imaging techniques can reveal changes of activity in the central nervous system by measuring the regional cerebral blood flow (rCBF). Only a few studies have yet applied these techniques to tinnitus to reveal such changes (Shulman et al., 1995; Cacace et al., 1996a; Arnold et al., 1996; Lockwood et al., 1998). The body of results from those studies suggests the existence of an abnormal connection between the auditory cortex and the limbic system. It is hypothesized that the auditory system mediating the tinnitus sensation may activate emotion control systems and memory systems in the hippocampus. Thus, the involvement of such brain regions may explain the distress and annoyance associated with many cases of tinnitus.

We studied the functional neuroanatomy of the generation, perception and processing of tinnitus with PET in a group of patients with disabling tinnitus. Our goal was to test the working hypothesis that effective masking and suppression of the tinnitus sensation with lidocaine is associated with a decreased activity in one or more cortical regions involved in the perception of the tinnitus stimulus. PET images of rCBF distribution were obtained while the subjects experienced their habitual tinnitus and while this sensation was suppressed or removed. By adopting the subtractive approach on these PET data sets, we expected to isolate activation in specific neuroanatomical systems concerned with the cerebral representation of tinnitus. Based on prior work and theoretical considerations, we predicted that the sensation of tinnitus would recruit the primary and associative auditory cortices in the temporal lobe, the prefrontal cortex and the limbic system. Thus, we anticipated to find further support for theories of tinnitogenesis.

2. Materials and methods

The protocol followed the Helsinki Declaration II and was approved by the Aarhus County Research Ethics Committee.

2.1. Subjects

12 Right-handed subjects (four females, eight males, aged 25–62 years, mean age 38 years) with severe chronic tinnitus as their primary complaint participated in the study. Three patients suffered from left-sided tinnitus, four had right-sided tinnitus and five had bilateral tinnitus. All patients were interviewed about details of their past history and the nature of their tinnitus. The alleged causes of tinnitus were noise exposure in six subjects, whiplash in one subject, diving in one subject and unknown origin in four subjects. The tinnitus symptom had persisted from 1 year to 12 years with an average of 4 years.

Each patient underwent complete otoneurological and audiological evaluations including pure-tone and speech audiometry, a pitch and loudness matching

test and tympanometry. Additionally, cardio-pulmonary examinations, including ECG, were performed to evaluate the subjects general medical fitness prior to the lidocaine administration. No abnormal findings were detected. Others than the otologic disorders, the subjects had no history of medical or neurological illnesses and were free from medication and drug abuse. Audiological testing and tinnitus matching were carried out in a sound-attenuating acoustic chamber using an Orbiter 922 (Madsen electronics) audiometer. A pitch and loudness match as well as the evaluation of the minimum masking level for tinnitus were obtained according to customary methods (Coles et al., 1984).

2.2. Scanning procedures and data acquisition

Using an ECAT Exact HR47 PE-tomograph (Siemens/CTI), cerebral activation was measured as change in the relative rCBF distribution as mapped by the radioactivity in the brain after the intravenous bolus injection of ^{15}O-labelled water (Raichle et al., 1983). Tomograms were obtained in a three dimensional (3-D) mode. A Ga-68 transmission tomogram in a two dimensional (2-D) mode of 10 min duration was obtained prior to administration of tracer and was used to correct emission scans for attenuation effects. Eight emission scans of a single 40 s frame were initiated at 60 000 true cps after bolus injection of 500 MBq $H_2^{15}O$. Using filtered back projection, each PET image was reconstructed after correction for attenuation and scatter resulting in a resolution of 18 mm FWHM (Hann-filter with a cut-off frequency of 0.15 cycles per s). The interscanning interval was 12 min. Subjects were scanned in a quiet, darkened room and lay supine, with their head fixed in a vacuum pillow. To anatomically localize sites of changed rCBF, individual T_1-weighted brain MR images were acquired prior to PET scans on a Philips 1.5 T Gyroscan, with Fast-Field-Echo sequence, 64 sagittal 2 mm slices, TE = 21.6 ms and TR = 41.7 ms. The individual MR images of the 12 subjects were pooled, co-registered and aligned to a standard brain obtained from 305 brain MR images.

2.3. Experimental procedure

Eight scans were completed for each subject (Table 1). During four PET scans, subjects had their tinnitus sensation suppressed by masking sounds presented through an E-A-R TONE 3A insert earphone in the tinnitus-affected ear or ears. An earplug was placed in the non-stimulated ear. The masking sounds consisted of narrow band noise of 1/3 octave and corresponded to the individual minimum masking level of each subject. The presentation of the masking stimuli started 10 s prior to scanning and lasted throughout the scan. To reduce tinnitus pharmacologically, lidocaine without vasoconstrictor and preservative was administered by intravenous (i.v.) injection through an infusion line in an antecubital vein. A solution of 1.5 mg/kg body weight lidocaine hydrochloride (Lidokain, SAD) diluted in normal saline (100 ml NaCl 0.9% w/v) was given as a bolus over a period of 5 min between scan 4 and 5. Thus, a typical subject weighing 70 kg received a total dose of 105 mg lidocaine. All experiments were conducted under continuous ECG and blood pressure monitoring. The different conditions were repeated twice, each for a total of eight scans. Scans 1 and 4 were used as the baseline condition with tinnitus sensation. The suppressed tinnitus conditions were masking (mask, scans 2 and 3), lidocaine (lido, scans 5 and 8) and influence of both masking sound and lidocaine (masklido, scans 6 and 7).

2.4. Data and image analysis

To correct for head movements between scans, all PET images were aligned with the Automated Image Reconstruction (AIR) software (Woods et al., 1992). PET and MRI data of each subject were individually co-registered (Collins et al., 1994) and the matched PET-MRI data sets were re-sampled in the standardized stereotaxic coordinate system of Talairach and Tournoux (1988).

To obtain volumes of the tinnitus-related change in rCBF for each subject, scans with suppressed or considerably reduced tinnitus were subtracted from those with tinnitus sensation (Table 2). Thus, an activation in a specific brain region after a subtraction of data sets indicates that this brain region is active during the perception of tinnitus (base) and not active during the tinnitus-suppressed conditions (mask, lido, masklido). The subtraction approach diminishes the problem of global activity. Basic brain activity, present in all conditions, is removed. The analyses were performed on all subjects and on two subgroups where subjects with bilateral tinnitus were combined with those with left- or right-sided tinnitus resulting in subgroups of eight and nine subjects, respectively. These subdivisions were made to reveal possible effects of laterality in activation.

The strict null hypothesis states that no difference exists between the PET data sets obtained during tinnitus sensation and during tinnitus suppression. The presence of significant changes in rCBF was tested by calculating a two-tailed *t*-statistic. A pooled S.D. after pixel by pixel subtraction of PET volumes and very large effective degrees of freedom (dependent on the correlation structure of the voxels) were used, allowing the approximation to a standard Gaussian distribution (*Z*-statistics) (Worsley et al., 1992). By searching the

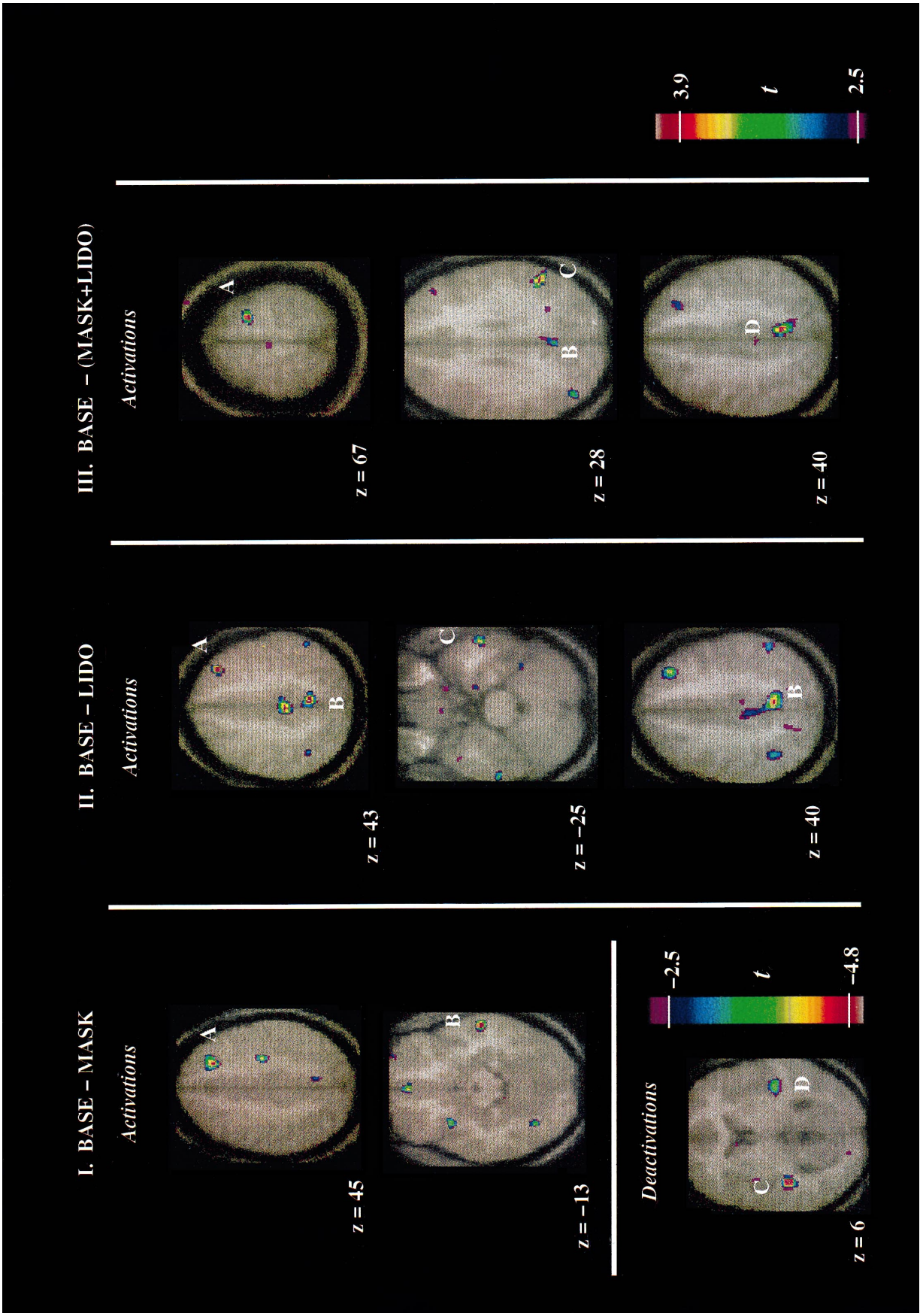
I. BASE – MASK
Activations
A
z = 45
B
z = –13
Deactivations
C
D
z = 6
II. BASE – LIDO
Activations
A
B
z = 43
C
z = –25
B
z = 40
III. BASE – (MASK+LIDO)
Activations
A
z = 67
B
C
z = 28
D
z = 40
–2.5
t
–4.8
3.9
t
2.5

Fig. 1. PET maps of brain activity associated with the perception of tinnitus. (I) Activated sites (t-statistic maps) in subtraction base−mask. Foci of increased activity in (A) the right middle frontal gyrus, (B) the right middle temporal gyrus and decreases of activity in (C) the left transverse temporal and (D) the right superior temporal gyri. (II) Selected t-statistic maps from subtraction base−lido. Foci of increased activity in (A) the right middle frontal gyrus, (B) the right precuneus and (C) the right middle temporal gyrus. (III) Selected t-statistic maps of activation sites in subtraction base−masklido. This combined suppression by masking sound and intravenous lidocaine contrasted to baseline (base−masklido) elicited foci of activation in (A) the right superior temporal gyrus, (B) the right posterior cingulate gyrus, (C) the right inferior parietal lobule and (D) the right precuneus. The t-maps are shown superimposed on trans-axial slices of average MR images of 12 subjects. Talairach coordinates and t-peak values of the activated sites are listed in Tables 3–5. For further details, see text.
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cerebral cortex (500 ml), t-values equal to or exceeding $t = 4.002$ were considered to represent significant ($P < 0.05$) changes in rCBF, corrected for multiple comparison.

3. Results

3.1. Subjects

Pure-tone audiograms showed that seven patients had high frequency sensorineural hearing loss in the affected tinnitus ear or ears. The hearing levels of these subjects at 250–2000 Hz were in the limits of normal hearing ability (hearing level better than 15 dB HL). At 4000 Hz, the hearing levels ranged from 20 to 40 dB HL with an average of 30 dB HL and at 8000 Hz, hearing levels ranged from 20 to 60 dB HL with an average of 40.5 dB HL. The remaining five subjects had normal hearing. Pitch matching showed an exclusively high frequency noise and/or pure-tone type tinnitus of above 2000 Hz. A loudness match revealed sensation levels between 5 and 15 dB SL.

All subjects had total tinnitus relief during the masking procedures. 10 Subjects (83%) were lidocaine responders with complete remission or considerable reduction of the severity of their tinnitus. The effect of lidocaine persisted throughout the scanning session, but faded away shortly after the procedures (between 10 and 30 min). No serious untoward effects were noticed. Transient vertigo or floating sensation were reported by five of the 12 subjects. The subjective hearing ability of all subjects remained unchanged.

3.2. PET results

All data analyses were performed on pooled data from all 12 subjects or on pooled data from specific subgroups, as indicated below. PET volumes obtained during the habitual tinnitus sensation were contrasted to tinnitus suppression conditions, revealing the mobilized functional units specific to the perception of tinnitus. For presentation, activated peaks were superimposed on aligned average MR images of the 12 subjects (Fig. 1).

3.2.1. Tinnitus condition minus masking condition (base−mask) (Table 3, Fig. 1I)

Two main rCBF increases were observed in the right middle frontal and the right middle temporal gyri. The subgroup of eight subjects with left or bilateral tinnitus revealed the same activities in the right-sided frontal and temporal sites, but showed an additional increase in the rCBF signal in the left superior temporal gyrus. The same patterns of right-sided temporal and frontal increases were found in the subgroup of nine subjects with right or bilateral tinnitus.

Decreases in the rCBF signal were revealed in the left transverse temporal gyrus (primary auditory cortex, BA 41) and in the right superior temporal gyrus in the analysis of all subjects, whereas only deactivations were seen in the primary auditory cortex on the left side in the two side-dependent subgroups.

3.2.2. Tinnitus condition minus lidocaine condition (base−lido) (Table 4, Fig. 1II)

The base−lido subtraction elicited activities in the

Table 1
Experimental design

Scan	Acoustic stimulus	Lidocaine effect	Tinnitus perception	Abbreviation
1	None	No	Present	Base
2	Masking sound	No	Absent	Mask
3	Masking sound	No	Absent	Mask
4	None	No	Present	Base
5	None	Yes	Absent	Lido
6	Masking sound	Yes	Absent	Masklido
7	Masking sound	Yes	Absent	Masklido
8	None	Yes	Absent	Lido

Masking sound (narrow band noise) individually adjusted to each subject's minimum masking level. Lidocaine administration between scan 4 and 5 as i.v. bolus injection of 1.5 mg/kg body weight over a period of 5 min.

Table 2
Subtractions of interest

Tinnitus present		Tinnitus absent
Base (scan 1+scan 4)	Minus	Mask (scan 2+scan 3)
Base (scan 1+scan 4)	Minus	Lido (scan 5+scan 8)
Base (scan 1+scan 4)	Minus	Masklido (scan 6+scan 7)

List of subtractions of PET volumes without tinnitus sensation from PET volumes with usual tinnitus sensation.

right middle frontal and right middle temporal gyri close to the sites in the previous subtraction. Other increases in the rCBF signal were observed in the right precuneus and the right paracentral lobule. Exclusion of the two lidocaine treatment non-responders from this calculation did not change the pattern appreciably. No decrease of activity occurred in this subtraction.

3.2.3. Tinnitus condition minus masking/lidocaine condition (base−masklido) (Table 5, Fig. 1III)

Subtraction of scans obtained under the combined influence of masking sound and lidocaine from scans with tinnitus sensation elicited activation in the posterior part of the right superior frontal gyrus, the right inferior parietal lobule, the right precuneus and the right posterior cingulate. The posterior part of the left transverse temporal gyrus (primary auditory cortex, BA 41) and a subcortical site in the left auditory radiation were deactivated.

4. Discussion

This study was designed to identify neuroanatomical systems which subserve the perception of tinnitus. The null hypothesis claimed that no difference exists between data sets obtained with tinnitus perceived and tinnitus suppressed. The hypothesis was rejected because several brain regions revealed differential activity with tinnitus perceived. The majority of sites were in the right hemisphere, regardless of the side to which the tinnitus was lateralized subjectively. The right hemisphere preponderance implies an asymmetry in the functional distribution of the involved brain structures. As expected, specific cortical fields of the prefrontal and temporal lobes were active during perceived tinnitus (base), but not during tinnitus-suppressed conditions (mask, lido, masklido). Thus, the data suggest that the perception of tinnitus is mediated by a specific network of functionally linked neural centers.

Comparison of the results of previous functional neuroimaging studies of tinnitus with the present results revealed that only some of the sites were coincident with previous maps. Differences in the experimental designs may be the reason for the discrepancies. Previous studies compared scans from patients with tinnitus to scans from normal subjects. A SPECT imaging study on patients with tinnitus demonstrated perfusion asymmetries bilaterally in temporal, frontal, parietal and hippocampal-amygdala regions (Shulman et al., 1995).

Table 3
Results from subtraction of the condition with suppressed tinnitus (masking) from the condition with habitual tinnitus sensation (base−mask)

Subtraction	Anatomical location	Talairach coordinates*			Brodmann area	*t*-value**
		x	y	z		
Base−mask (whole group of subjects, $n=12$)						
Activations	Right middle frontal gyrus	24	25	45	8	3.5
	Right middle temporal gyrus	60	−18	−13	21	3.8
Deactivations	Left transverse temporal gyrus	−38	−31	6	41	−4.4
	Right superior temporal gyrus	56	−26	12	42/22	−3.4
Base−mask (left-sided and bilateral tinnitus, $n=8$)						
Activations	Right middle frontal gyrus	38	24	27	9	3.4
	Right middle temporal gyrus	59	−18	−13	21	3.6
	Left superior temporal gyrus	−29	3	−33	38	3.5
Deactivations	Left transverse temporal gyrus	−38	−30	6	41	−4.2
	Left inferior parietal lobule	−36	−61	45	7	−3.4
Base−mask (right-sided and bilateral tinnitus, $n=9$)						
Activations	Right middle frontal gyrus	24	25	45	8	3.0
	Right middle temporal gyrus	60	−21	−9	21	3.6
	Left precentral gyrus	−4	−28	72	4	3.9
	Left fusiform gyrus	−31	−66	−10	19	3.3
Deactivations	Left transverse temporal gyrus	−38	−31	9	41	−3.6
	Left thalamus	−7	−18	−16	–	−4.0
	Left post-central gyrus	−36	−31	67	1	−3.7

*Talairach coordinates in mm: x (medial-lateral position relative to midline, right (+)/left (−)), y (anterior-posterior position relative to anterior commissure, anterior (+)/posterior (−)) and z (superior-inferior position relative to the intercommissural plane, superior (+)/inferior (−)).
**Significance level is given in *t*-test units.

Table 4
Results from subtraction of the condition with suppressed tinnitus (lidocaine) from the condition with habitual tinnitus sensation (base−lido)

Subtraction	Anatomical location	Talairach coordinates*			Brodmann area	*t*-value**
		x	y	z		
Base−lido (whole group of subjects, $n=12$)						
Activations	Right middle frontal gyrus	32	30	43	8	3.3
	Right middle temporal gyrus	60	−7	−25	21	3.0
	Right precuneus	8	−52	40	7	3.6
	Right paracentral lobule	3	−28	48	5	3.8
Base−lido (lidocaine responders, $n=10$)						
Activations	Right middle frontal gyrus	32	30	43	8	3.0
	Right precuneus	9	−52	39	7	3.4
	Right paracentral lobule	6	−28	55	5	3.1
	Right angular gyrus	42	−73	31	39	3.2

*Talairach coordinates in mm: x (medial-lateral position relative to midline, right (+)/left (−)), y (anterior-posterior position relative to anterior commissure, anterior (+)/posterior (−)) and z (superior-inferior position relative to the intercommissural plane, superior (+)/inferior (−)).
**Significance level is given in *t*-test units.

Comparable normative brains showed no such abnormalities. The activations in temporal and prefrontal sites were similar to ours. The authors hypothesized that the additional activations in the thalamus, hippocampus and amygdala may be a correlate of affect components and of a paradoxical auditory memory of tinnitus. An fMRI study compared the neural activity in three tinnitus patients to two normal controls. Tinnitus-related activity was found in the upper brainstem and frontal cortex in two of three tinnitus sufferers, but not in the controls (Cacace et al., 1996a, b; Cacace, 1997). A [^{18}F]fluorodeoxyglucose (FDG) PET study compared 11 patients with tinnitus (10 with tinnitus on the right side, one with tinnitus on the left side) to 14 healthy control individuals and found a significantly increased metabolic activity in the primary auditory cortex (PAC) in nine out of 10 patients with right-sided tinnitus (Arnold et al., 1996). These activations were not found in the present study. Another PET study with ^{15}O-water as the tracer examined tinnitus patients able to alter the perceived loudness of the tinnitus by oro-facial movements. That study revealed foci of increased activity in the left middle temporal, left transverse temporal gyri, hippocampus and thalamus (Lockwood et al., 1998). Increased rCBFs in these structures were found by comparing scans of tinnitus perception in patients with scans without tinnitus perception in healthy controls and by comparing scans of the rest state (habitual tinnitus) with the stimulated state (aggravated tinnitus by oro-facial movements) in patients. The comparison of the effect of a 2 kHz pure-tone on patients and normal volunteers revealed activities in the right middle temporal and superior temporal gyri, close to the sites found in the present study. The authors hypothesized that the neural systems involved in tinnitus generation may also mediate the control of emotions and memory functions and that a considerable reorganization of the auditory cortex may explain the expanded area of activation during processing of external auditory stimuli.

In summary, results from several studies indicate that the sensation of tinnitus may involve the auditory cortex, the limbic system and different frontal brain re-

Table 5
Results from subtraction of the condition with suppressed tinnitus (masking+lidocaine) from the condition with habitual tinnitus sensation (base−masklido)

Subtraction	Anatomical location	Talairach coordinates*			Brodmann area	*t*-value
		x	y	z		
Base−masklido (whole group of subjects, $n=12$)						
Activations	Right superior frontal gyrus	19	−4	67	6	3.7
	Right supramarginal gyrus	53	−47	28	40	3.6
	Right precuneus	8	−52	40	7	3.6
	Right posterior cingulate	1	−57	24	31	3.5
	Left middle occipital gyrus	−40	−73	24	19	3.7
	Right inferior parietal lobule	51	−45	25	40	3.6
	Cerebellum	17	−45	−18	−	4.0
Deactivations	Left transverse temporal gyrus	−38	−40	13	41	−3.6
	Auditory radiation	−35	−26	6	−	−3.6

*Talairach coordinates in mm: x (medial-lateral position relative to midline, right (+)/left (−)), y (anterior-posterior position relative to anterior commissure, anterior (+)/posterior (−)) and z (superior-inferior position relative to the intercommissural plane, superior (+)/inferior (−)).

gions. Thus, not only 'simple' auditory processing, but also specific higher order cognitive elaboration may be involved.

Clinical observation and assessment of tinnitus by different psychological and disease-specific tests suggest that attention may be the cognitive mechanism underlying tinnitus annoyance and distress (Newman et al., 1997). We speculate that the interpretation of an internally generated stimulus as bothersome may engage the same agents as the response to a novel externally generated stimulus. The purpose of the response to such a stimulus is orientation or attention (McKenna, 1997). An indifferent and/or repeatedly presented stimulus is habituated and the strength of the behavioral response declines. An important stimulus from a pleasant or threatening experience maintains the attention. Memory, which relates the new stimulus to previous experiences, may play an important role in this process too. Thus, the threat to personal integrity (fear of having tinnitus the rest of the life, fear of a potentially lethal disease causing the tinnitus, etc.) could lead to different neurophysiological mechanisms militating against normal habituation and potentiating the annoying effect by enhancement of negative beliefs (Jastreboff, 1990; Hazell, 1995; Sheldrake et al., 1995; Jastreboff, 1996a; Jastreboff et al., 1996b).

To evaluate and interpret the consistently prefrontal activations in the right hemisphere in the present study, comparison to a sufficiently large body of information from cognitive brain studies is necessary. The prefrontal cortex and the limbic system control attention, memory and the emotional state (Chronister and Hardy, 1997; Tzourio et al., 1997). Attention engages several subsystems, but independently of the stimulus modality and subsystem involved, many studies revealed coincident maps of activation. An fMRI study of selective auditory attention revealed an increased activity in the right middle frontal, the right middle temporal gyri, the precuneus, the posterior cingulate and the right inferior parietal lobule (Pugh et al., 1996). In the present experiments, we subtracted scans obtained with tinnitus suppressed by lidocaine from baseline scans and found similar sites of activation (Table 4, 5). In the study of Pugh et al. (1996), the prefrontal and temporal sites were located within a distance of approximately 10 mm from the sites of peak activity in the present study, but the posterior sites were less spatially consistent. In another study, PET mapping of the neuronal correlates of sustained attention to somatosensory stimuli revealed sites of increased activity in the same prefrontal, temporal and parietal areas, but found additional activation in the cerebellum close to the site in this study (Pardo et al., 1991). A different correlate of selective auditory attention in patients with tinnitus was elaborated in a study of endogenous event-related potentials (ERP) (Jacobson et al., 1996). The electrophysiological signal related to attention had a significantly greater magnitude in tinnitus sufferers than in subjects without tinnitus. The altered electrophysiological signals were claimed to originate in the supratemporal plane, superior temporal gyrus, thalamus and frontal lobe. Activation of the prefrontal and associative auditory areas as well as the activation of the precuneus in the present study agree with these findings.

Several studies were designed to uncover the central mechanisms of memory processing. The stimuli used were different visual and auditory signals with tasks involving active mental manipulation or maintenance. A majority of these studies yielded converging evidence of prefrontal activation (Zatorre et al., 1994; Buckner et al., 1995; Fletcher et al., 1995a, b; Kapur et al., 1995; Fiez et al., 1996; Lewin et al., 1996; Klingberg et al., 1996; Zorrilla et al., 1996; Cohen et al., 1997). Many peaks of increased neural activity were located within reasonable proximity (<15 mm) of the sites of activation in the right middle frontal gyrus noted in the present study (Table 3, 4). The right precuneus and the right inferior parietal lobule were activated in studies testing the retrieval of multimodally presented material (focused episodic memory) (Grasby et al., 1994; Shallice et al., 1994; Andreasen et al., 1995; Fletcher et al., 1995b; Kapur et al., 1995; Fletcher et al., 1996). Many of the peaks described in these studies were close to the activated posterior sites in the two present subtractions involving lidocaine (Tables 4, 5).

An early study on the surgical treatment of 20 tinnitus sufferers described the effect of frontal lobotomy as further evidence for a role of the frontal lobe in the maintenance of severe tinnitus. After surgery, the severity of the tinnitus declined in all patients and the perceived loudness decreased in approximately half of the patients (Beard, 1965). Support for the hypothesis of cortical generation or aggravation of tinnitus was obtained in reports on the outcome of surgical treatment of acoustic neuroma. Post-operatively, the majority of patients with pre-operative tinnitus retained tinnitus sensation, despite sectioning of the eighth cranial nerve (Parving et al., 1992; Vanleeuwen et al., 1996; Andersson et al., 1997; Rigby et al., 1997). Other surgical invasions of the inner ear or eighth cranial nerve gave similar results (House, 1981; Sakai et al., 1995). Thus, the removal of an assumed trigger or source of tinnitus in the periphery (cochlea, acoustic nerve, etc.) did not eliminate its perception.

Most tinnitus signals are acoustically weak although they adversely affect the patients' lives. Audiometric assessment shows that most matches to loudness ($>85\%$) characteristically do not exceed 10 dB (Meikle and Taylor-Walsh, 1984; Hulshof, 1986; Feldmann, 1992; Jakes, 1997). The loudness of ipsilaterally pre-

sented masking sounds usually has to be only slightly stronger than the matched loudness of the tinnitus sound. Masking of an externally presented sound by another sound presented in the opposite ear requires much higher levels of intensity of the masking sound. A characteristic feature of tinnitus is the masking by sounds presented to the contralateral ear with intensities only slightly higher than the intensity of the tinnitus itself and unable to cross the skull (Feldmann, 1984). We expected subtraction of data from scans obtained during the presentation of a masking sound (stronger auditory stimulus) from data from scans obtained during perceived tinnitus (weaker auditory stimulus) to reveal a decrease in the rCBF signal in the primary auditory cortex (Heschl's gyrus, BA 41). This deactivation was consistently found in the left transverse temporal and right superior temporal gyri in the present study.

Intravenously administered, lidocaine causes temporary tinnitus relief in 70–80% of patients so treated (Barany, 1935; Melding et al., 1978; Shea and Harell, 1978; Perruca and Jackson, 1985; Merchant and Kirtane, 1986; Schmidt et al., 1994). In this study, the positive response to lidocaine was 83%. Whether lidocaine acts at the level of the cochlea, the auditory nerve, the brainstem or in the cortex is not known (Merchant and Kirtane, 1986; Murai et al., 1992; Møller, 1984), but most probably, lidocaine alters the tinnitus signal by inhibition of neurotransmission. Thus, lidocaine and masking sounds suppress the generation or perception of tinnitus at different cerebral sites and levels and by different mechanisms. Therefore, we expected the combination of masking sound and lidocaine to result in somewhat different activation, compared to the activation elicited in the individual masking and lidocaine scans. In fact, the third subtraction of interest (base−masklido) did not reveal activity in the right middle frontal and right middle temporal gyri. The only right prefrontal activation occurred in the superior frontal gyrus localized more rostrally, medially and posteriorly. Two posterior midline structures, the posterior cingulate and the precuneus, and the right inferior parietal lobule were also activated.

A recent report describing the inhibitory effect of lidocaine on the salicylate-induced increased discharge rate in auditory nuclei of guinea pigs, which is believed to be the neurophysiological correlate of tinnitus in animals, points to an involvement of the auditory brainstem nuclei (inferior colliculus) in tinnitus generation (Manabe et al., 1997). Other animal studies testing the effects of salicylate on the [^{14}C]2-deoxyglucose uptake and on the expression of the proto-oncogene c-fos as a correlate of neural activity showed that the activity in the inferior colliculus was low, while regions localized more centrally showed an increased activity (Wallhäusser-Franke et al., 1996; Wallhäusser-Franke, 1997). Also, these results point to a central network active in the generation of tinnitus.

On the basis of these results, we find support for a theory of central processing, exacerbation or generation of disabling tinnitus. The tinnitus sensation is hypothesized to depend on perception of an aberrant auditory sensory input (spontaneous or pathological signals from within the auditory pathways), which is modified by prior auditory knowledge (involvement of memory systems). Tinnitus may be associated with an inappropriate allocation of attentional resources, which maintain a sustained state of alertness. The similarity of our findings to foci found in earlier studies on attention and memory is consistent with the hypothesis of the involvement of these central networks in the generation and maintenance of tinnitus distress.

In an alternative hypothesis, we may speculate that tinnitus perception and generation instead of being purely hierarchical (bottom-up, i.e. aberrant signal created peripherally, transmitted to subcortical and cortical centers, causing perception and emotional responses), in some cases, are the results of a spontaneous pathologic interaction between non-auditory association centers, emotional centers and sensory processing areas, which do not receive any sensory input from the periphery (top-down) (Frith and Dolan, 1997). The auditory sensation may be secondary to the initial development of neurophysiologic pathologies or reorganization of these centers.

Self-generated sensory imagery may depend on prior expectations of the perception (memory) and may involve activation of modality-specific sensory sites (i.e. auditory cortices). Support for this hypothesis came from a recent study that used magnetic source imaging for the determination of differences in tonotopy in the auditory cortex of tinnitus patients and normal volunteers (Mühlnickel et al., 1998). The study demonstrated that tinnitus is associated with a change of the tonotopic map based on reorganization of the auditory sensory cortex. Similar reorganization of sensory cortices was observed in studies of cortical changes after limb amputation and development of phantom pain (Elbert et al., 1994). Further support for a hypothesis of auditory imagery underlying tinnitus generation came from a PET study of musical imagery and perception (Zatorre et al., 1996). This study showed that both perception and imagery (including pitch analysis of specific auditorily presented and imagined tonal targets) produced similar patterns of brain activity. Sites of activation were among others bilaterally located in associative auditory cortices and in the right prefrontal area. The auditory sensory cortex in the right hemisphere is believed to be linked to pitch processing, whereas the right prefrontal lobe is believed to be associated with pitch

retention in tasks involving comparison of different sounds (Zatorre and Samson, 1991; Zatorre et al., 1992). Thus, activation of these brain areas may also be responsible for the generation of the auditory phantom perception which is tinnitus.

A fMRI study of auditory hallucinations reported foci of strong activation in primary and associative auditory areas during auditory phantom experiences (David et al., 1996). A recent PET study comparing functional brain maps obtained during normal hearing, imaginary hearing and auditory hallucination found increased rCBF signals in the auditory association cortex and the anterior cingulate (BA 32) in both normal hearing and during hallucination (Szechtman et al., 1998). The authors suggest that the right anterior cingulate cortex may be the site in the brain responsible for producing auditory hallucinations. Reports on auditory hallucinations in schizophrenia describe activation of 'executive' prefrontal sites together with auditory association areas (Cleghorn et al., 1990; Frith, 1996; Woodruff et al., 1997), others of increased activity in limbic structures and the thalamus (Silbersweig et al., 1995). With regard to tinnitus, we hypothesize that the auditory phantom perception in some cases emanates from a pathologic activation of cortical and/or subcortical systems without the need for a stimulus from an origin peripheral to the auditory pathways.

5. Conclusion

While the generator of tinnitus may be located peripherally or centrally, the perception, further processing and interpretation all take place centrally. The increased rCBF at the different brain sites revealed in the present study support this hypothesis and suggests that disabling and distressing tinnitus is associated with activity in functionally linked cortical areas subserving the processing of auditory signals, memory and attention. Severe tinnitus represents a failure of habituation which maintains the activation of brain regions normally engaged in interaction with the exterior environment. In some cases, tinnitus may be generated internally without a source peripheral to the central auditory system (e.g. cochlea). Reorganization of brain processes, by means of plasticity of brain functions, may underlie these changes.

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