Review Article

Neural activity underlying tinnitus generation: Results from PET and fMRI

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ABSTRACT

Tinnitus is the percept of sound that is not related to an acoustic source outside the body. For many forms of tinnitus, mechanisms in the central nervous system are believed to play an important role in the pathology. Specifically, three mechanisms have been proposed to underlie tinnitus: (1) changes in the level of spontaneous neural activity in the central auditory system, (2) changes in the temporal pattern of neural activity, and (3) reorganization of tonotopic maps. The neuroimaging methods fMRI and PET measure signals that presumably reflect the firing rates of multiple neurons and are assumed to be sensitive to changes in the level of neural activity. There are two basic paradigms that have been applied in functional neuroimaging of tinnitus. Firstly, sound-evoked responses as well as steady state neural activity have been measured to compare tinnitus patients to healthy controls. Secondly, paradigms that involve modulation of tinnitus by a controlled stimulus allow for a within-subject comparison that identifies neural activity that may be correlated to the tinnitus percept. Even though there are many differences across studies, the general trend emerging from the neuroimaging studies, is that tinnitus in humans may correspond to enhanced neural activity across several centers of the central auditory system. Also, neural activity in non-auditory areas including the frontal areas, the limbic system and the cerebellum seems associated with the perception of tinnitus. These results indicate that in addition to the auditory system, non-auditory systems may represent a neural correlate of tinnitus. Although the currently published neuroimaging studies typically show a correspondence between tinnitus and enhanced neural activity, it will be important to perform future studies on subject groups that are closely matched for characteristics such as age, gender and hearing loss in order to rule out the contribution of these factors to the abnormalities specifically ascribed to tinnitus.

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1. Introduction

1.1. Tinnitus definition and prevalence

Tinnitus is an auditory sensation without the presence of an external acoustic stimulus. Almost all adults have experienced some form of tinnitus, mostly transient in nature, at some moments during their life. However, in 6–20% of the adults, tinnitus is chronic and for 1–3% tinnitus severely affects the quality of life. Tinnitus is more prevalent in men than in women and its prevalence increases with advancing age (Axelsson and Ringdahl, 1989; Lockwood et al., 2002).

Tinnitus can be differentiated into subjective and objective tinnitus. In objective tinnitus, sound from the body leads to an auditory percept via normal hearing mechanisms, i.e. by stimulation of the hair cells in the inner ear. Consequently, objective tinnitus is not a true hearing disorder in the sense that the hearing organ is affected. Rather, normal perception of an abnormal sound source in the body (somatosound) causes the complaint. Typically, sources of objective tinnitus are of vascular or muscular origin. Due to vascular anomalies (Chandler, 1983), vibrations due to pulsatile blood flow near the middle or inner ear (Weissman and Hirsch, 2000; Liyanage et al., 2006; Sonmez et al., 2007) can become audible. Also, involuntary contraction of muscles in the middle ear (Abdul-Baqi, 2004; Howsam et al., 2005) or in palatal tissue (Fox and Baer, 1991) may cause objective tinnitus. Objective tinnitus is rare and has been described only in case reports.

Subjective tinnitus is far more common than objective tinnitus. In contrast to objective tinnitus, there is no (overt) acoustic stimulus present in cases of subjective tinnitus. Like any acoustic

percept, tinnitus must be associated with activity of neurons in the central auditory system; abnormal tinnitus-related activity may arise from abnormal cellular mechanisms in neurons of the central auditory system, or may result from aberrant input from the cochlea or non-auditory structures.

The distinction between objective and subjective tinnitus (Møller, 2003; Lockwood et al., 2002) is debatable (Jastreboff, 1990) in a sense that it is based on whether a somatosound can be detected or objectified by an external observer, rather than on the possible underlying mechanisms. As far as we can tell, all neuroimaging studies reviewed in this paper describe results for tinnitus where there is no objective sound source. In other words, this review is about subjective tinnitus.

1.2. Tinnitus and the central auditory system

Subjective tinnitus is often associated with peripheral hearing loss (Eggermont and Roberts, 2004; Nicolas-Puel et al., 2006), although tinnitus with no or minor hearing loss has also been reported (Stouffer and Tyler, 1990; Jastreboff and Jastreboff, 2003). Many patients describe tinnitus as a sound in one or both ears. Therefore, it has been thought for many years that the tinnitus-related neural activity must also originate from a peripheral source, i.e. the cochlea.

Some clinical observations indicate however, that a peripheral origin of tinnitus cannot account for all forms of tinnitus. In patients that underwent sectioning of the eighth cranial nerve as part of retro-cochlear tumor surgery, tinnitus arose in 34% of the cases (Berliner et al., 1992). Apparently, tinnitus may arise by disconnecting the cochlea from the brain. Sectioning of the eighth cranial nerve has also been applied in tinnitus patients in an effort to provide relief of the tinnitus. This was however not successful in 38–85% of cases (varying from 38% as reported by Barrs and Brackmann (1984) to 85% as reported by House and Brackmann (1981); reviewed earlier by Kaltenbach et al. (2005)). Clearly, in these cases, where the cochlea is disconnected from the brain, central mechanisms must be responsible for the tinnitus.

Evidence for changes in the firing pattern of neurons in the central auditory system as possible substrate of tinnitus is supported by research on tinnitus using animal models. Noise trauma and ototoxic drugs, which are known to cause peripheral hearing loss and tinnitus in humans, result in behavioral responses in animals that are consistent with the presence of tinnitus (reviewed in Eggermont and Roberts (2004)). These manipulations also result in changes of spontaneous neural activity in several auditory brain centers. For example, noise-induced trauma decreases spontaneous firing rates (SFRs) in the eighth cranial nerve and increases the SFRs at several levels in the auditory brainstem and cortex (Noreña and Eggermont, 2003; Kaltenbach et al., 2004). Other possible neural correlates of tinnitus that have been investigated are changes in burst firing and neural synchrony (Noreña and Eggermont, 2003; Seki and Eggermont, 2003). Apparently, peripheral hearing loss results in a reduction of afferent input to the brainstem, which leads to changes in neural activity of the central auditory system, hereby causing tinnitus.

In addition to these possible changes in spontaneous neural activity, cortical tonotopic map reorganization has been recognized as possible neural correlate of tinnitus (Muhlnickel et al., 1998; Seki and Eggermont, 2003; Eggermont, 2006). All of the above may occur as a consequence of an imposed imbalance between excitation and inhibition in the auditory pathway.

None of the proposed mechanisms has been proven unequivocally as a substrate of tinnitus in humans. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are imaging modalities that can be used to study neural activity in the human brain. Both techniques can assess some aspects of human brain activity and, hence, may identify mechanisms that underlie the generation of tinnitus in humans. This review focuses on the application of these two functional imaging methods and summarizes and discusses results of studies that use these methods to study tinnitus.

2. Functional imaging methods

2.1. Introduction

Functional imaging methods are used to study dynamic processes in the brain and localize brain areas involved in perception or cognition. Various methods are available that differ in spatial resolution, temporal resolution and their degree of invasiveness and can measure several important aspects of hypothesized tinnitus-related changes in neural activity.

Electroencephalography (EEG) and magnetoencephalography (MEG) are non-invasive methods that respectively measure the electrical and magnetic fields, resulting from (synchronized) firing of neurons. These techniques have a high temporal resolution ($\sim$1 ms) and a spatial resolution in the order of 1 mm. EEG and MEG can – given their high temporal resolution – give detailed insight in the temporal aspects of brain dynamics and may, for example, be used to assess possible tinnitus-related differences in neural synchrony (Seki and Eggermont, 2003; Noreña and Eggermont, 2003). In humans, power differences in the spectrum of the EEG and MEG signal in subjects with tinnitus compared to control subjects were reported (Weisz et al., 2005a,b; Llinas et al., 2005).

This review focuses on the results of studies that have used positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in finding neural correlates of tinnitus in humans. Both methods measure signals that are only indirectly related to the magnitude of neural activity. A change of neuronal activity alters the local metabolism and perfusion of the brain (Raichle, 1998; Gusnard et al., 2001; Raichle and Mintun, 2006). PET mainly measures a change in regional cerebral blood flow (rCBF), while most fMRI methods register a blood oxygen level dependent (BOLD) signal. In addition to BOLD-fMRI, other fMRI methods are available that are based on e.g. arterial spin labeling (Detre et al., 2002) or vascular space occupancy (Lu et al., 2003). These methods, however, have not yet been used to assess tinnitus.

The most important information obtained from these techniques are the location, the extent and the magnitude of neural activity. Therefore, the question that may be addressed by the application of fMRI and PET is: which brain regions have an abnormal amount of neural activity in tinnitus subjects?

2.2. Positron emission tomography

PET imaging measures the regional cerebral blood flow (rCBF), using the uptake of a radioactive tracer injected in the blood circulation. An increase in neural activity causes the blood flow to increase regionally in response to a higher oxygen and glucose demand. The radioactive decay of the tracer results in the emission of photons, which are detected by the PET-scanner.

There are some limitations in using PET. By using radioactive tracers, ionization is induced in the human body, making it less suitable for repeated measurements of single subjects. A second limitation is the limited temporal resolution. The temporal resolution, which is determined by the half-life time of the employed tracer, is at best 2 min when using labeled water ($H_2^{15}O$). Data is accumulated throughout this period and hence, no inferences can be made on a smaller timescale. A change of experimental condition within this period is not practically feasible. In addition, there is a limited spatial resolution due to the size of the detectors (4–5 mm). An additional inherent limitation to the spatial resolution

is determined by the maximum free path of a positron before annihilation takes place, which varies from 2.4 mm (^{18}F) to 8.2 mm (^{15}O) in water (Weber et al., 2003).

An important advantage of PET, especially for auditory research is that it is a silent imaging technique. Hence, interference of the scanner noise with the experimental design is minimized (Johnsrude et al., 2002; Ruytjens et al., 2006). Moreover, in contrast to fMRI, patients with implants containing metal (e.g. cochlear implants) can safely participate in PET studies. Finally, steady state measurements can be made using PET for which fMRI is not suitable (see Section 3).

2.3. Functional magnetic resonance imaging

Functional MRI is another method to measure neural activity in the human brain. In short, hydrogen nuclei (protons) in the body display magnetic resonance behavior in the presence of the strong magnetic field of an MRI scanner. In MRI acquisitions, nuclei are exited by an electromagnetic pulse and their behavior after this pulse is characterized by two relaxation times: $T1$ and $T2/T2^*$. These time constants and the density of mobile protons are properties of the tissue and determine the local signal intensity. Differences in these properties determine the contrast in an MR image between various types of tissue.

Functional MRI relies on the difference in magnetic properties of oxygenated and de-oxygenated blood. During an fMRI experiment, task-related increases in neural activity and metabolism lead to an increase in CBF. The local increase in available oxygen however exceeds the need for oxygen. As a result, the amount of oxygen in the blood increases in the area associated with the oxygen need. Hemoglobin contains a ferrous core that changes with respect to its magnetic properties when it binds to oxygen. The change in oxygenation level will therefore lead to a change in the magnetic susceptibility of blood, leading to a change in the MR signal (Ogawa et al., 1990). The combination of increased rCBF accompanied with an increased blood oxygen level leads to a blood oxygen level dependent (BOLD) effect. This effect is used as contrast mechanism in functional MR imaging. Therefore, like PET, fMRI provides an indirect measure of neuronal activity.

A major limitation – especially in auditory research – is the acoustic noise produced by the scanner. During scanning, the MR scanner typically produces over 100 dB (SPL) of acoustic noise, making it difficult to segregate responses to experimental (auditory) stimuli from those to ambient scanner noise. A partial solution is the use of a sparse temporal sampling design (Hall et al., 1999), where a silent gap is inserted between successive scans, giving enough 'silence' to present experimental stimuli to subjects and detect the response even with low sound pressure level stimuli (Langers et al., 2007).

In addition to the produced acoustic noise, there are a number of contraindications for MRI research in humans. These contraindications include the presence of metal implants in the body. The fast switching of the magnetic fields in the MRI scanner may produce heat in the implant. Also, magnetic forces may cause dislocation of implants. These disadvantages make fMRI unsuitable for studies that aim to evaluate the effect of electrical implants for the treatment of tinnitus.

The main advantages of using fMRI compared to PET are the higher temporal resolution as well as the lack of ionizing radiation. This last point makes longitudinal studies of subjects possible. See Logothetis (2008) for a more in-depth review on fMRI.

3. Neuroimaging and tinnitus

Studies in animal models of tinnitus indicate that tinnitus may be related to abnormal spontaneous firing rates (SFRs) in auditory neural structures (Noreña and Eggermont, 2003; Seki and Eggermont, 2003). Unfortunately, some current neuroimaging techniques, especially fMRI, do not allow for the direct measurement of spontaneous firing rates. When using fMRI, there is an inherent signal from gray matter, white matter and cerebral spinal fluid depending on the imaging sequence used. These signals are based on tissue properties rather than a measure of neural activity like the uptake of oxygen ($[H_2^{15}O]$-PET) or glucose (FDG-PET) in PET imaging. The signal values as measured with fMRI can therefore not be quantified easily and thus, a value of an absolute baseline (a possible equivalent of spontaneous firing rates) cannot be determined.

Instead, fMRI relies mostly on the modulation of neural activity by some controlled experimental condition. Also PET, in combination with a tracer that has a short half-life time, can be used to measure differential activity. By measuring either rCBF with PET, or BOLD signals with fMRI in two (or more) conditions, differences between states (within single subjects) can be detected and may be used to assess neural activity (Ogawa et al., 1990).

Several paradigms have been applied to assess neural correlates of tinnitus. One method employs sound stimuli and measures sound-evoked responses. Then, possible mechanisms related to tinnitus are inferred from the measured responses in the central auditory pathway. A second method relies on the ability of a subgroup of subjects with tinnitus to manipulate their tinnitus by somatic modulation. Examples discussed here are jaw protrusion and cutaneous-evoked tinnitus. A third method is rapid change of gaze or tonic lateral gaze causing or modulating tinnitus. The fourth method is based on pharmaceutical intervention that causes a temporal change of the tinnitus (e.g. lidocaine). Finally, in a subcategory of subjects, tinnitus is temporarily reduced following the offset of an external acoustical stimulus (Terry et al., 1983; Roberts, 2007). This phenomenon is referred to as residual inhibition and may also be used as the basis of an experimental paradigm in functional imaging experiments. In all these paradigms neural activity is altered by the presentation of an external stimulus or by some manipulation that changes the perceptual characteristics of tinnitus. These may result in a measurable change in signal between experimental conditions.

In addition to this differential (within-subjects) method of measuring neural activity, PET imaging can be used to assess possible changes in steady state levels of neural activity. PET signals (i.e. rCBF) can be scaled to a standardized mean value for the whole brain (using e.g. grand mean scaling), enabling a between-subjects approach to assess possible tinnitus-related differences between subject groups.

Although conventional BOLD fMRI cannot easily be used to assess spontaneous neural activity (like SFRs), there are new potential methods developed that may assess baseline levels. One of these studies makes use of CO_2, saturating the BOLD response completely, therefore providing a ceiling-level that might be used as a reference to assess baseline levels of activity (Haller et al., 2006). These techniques however have not yet been used to study tinnitus.

In this review, neuroimaging experiments on tinnitus are grouped on the basis of their experimental paradigm and discussed accordingly. It has become evident from these experiments that various brain areas play a role in tinnitus. In the discussion section, an overview will be given of these areas and their importance in tinnitus. Given the various definitions of (especially) cortical auditory areas we adopt the following nomenclature: The primary auditory cortex (PAC) corresponds to Brodmann area 41 (BA 41), the secondary auditory cortex corresponds to BA 42 and the auditory association cortex corresponds to BA 21, 22 and 38. For each study we interpret the results based on the Brodmann nomenclature regardless of the nomenclature used by the authors themselves. In many

Table 1
Summary of the studies included in this review.

Number[a]	Reference	Imaging modality	Experimental design	Controls/patients	Tinnitus	Matching criteria[b]	
						Hearing loss	Age
1	Melcher et al. (2000)	fMRI 1.5T	Sound-evoked	6/7	4 lateralized/3 nonlateralized	y	y
2	Melcher et al. (2005)	fMRI 1.5T	Sound-evoked	14/17	?	y	?
3	Lanting et al. (2008)	fMRI 3T	Sound-evoked	12/10	10 lateralized	Only lf[c]	n
4	Smits et al. (2007)	fMRI 3T	Sound-evoked	10/42	35 lateralized/7 nonlateralized	n	n
5	Kovacs et al. (2006)	fMRI 3T	Sound-evoked	13/2	2 lateralized	n	n
6	Lockwood et al. (1998)	PET H$_2^{15}$O	Somatosensory modulation	6/4	4 lateralized	n	n
7	Cacace et al. (1999a)	fMRI 1.5T	Somatosensory modulation	0/1	Lateralized	d	–
8	Giraud et al. (1999)	PET H$_2^{15}$O	Gaze-evoked tinnitus	0/4	4 lateralized (deafferentiated ear)	–	–
9	Lockwood et al. (2001)	PET H$_2^{15}$O	Gaze-evoked tinnitus	7/8	8 lateralized (deafferentiated ear)	n	y
10	Staffen et al. (1999)	SPECT Xe^{133}	Lidocaine	0/1	Nonlateralized	–	–
11	Mirz et al. (1999)	PET H$_2^{15}$O	Lidocaine	0/12	7 lateralized/5 nonlateralized	–	–
12	Mirz et al. (2000a)	PET H$_2^{15}$O	Lidocaine	0/8	4 lateralized/4 nonlateralized	–	–
13	Andersson et al. (2000)	PET H$_2^{15}$O	Lidocaine	0/1	Nonlateralized	–	–
14	Reyes et al. (2002)	PET H$_2^{15}$O	Lidocaine	3/9	3 lateralized/6 nonlateralized	Only lf[c]	n
15	Plewnia et al. (2007)	PET H$_2^{15}$O	Lidocaine	0/9	1 lateralized/8 nonlateralized	–	–
16	Arnold et al. (1996)	PET FDG	Steady state	14/11	8 unilateral/2 bilateral	n	?
17	Wang et al. (2001)	PET FDG	Steady state	10/11	8 lateralized/3 nonlateralized	n	y
18	Langguth et al. (2006)	PET FDG	Steady state	0/20	16 lateralized/4 nonlateralized	–	–
19	Shulman et al. (1995)	SPECT Tc^{99}	Steady state	0/2	?	–	–
20	Osaki et al. (2005)	PET H$_2^{15}$O	Residual inhibition	0/3	3 nonlateralized	–	–

[a] Corresponding to numbers appearing in Table 2.
[b] Groups were matched according to criteria hearing loss and age; y, yes; n, no; ?, unknown; –, not applicable.
[c] Only matched at low-frequency (lf, 250–2000 Hz).
[d] Asymmetrical hearing loss.

cases, the Brodmann areas were given but in some cases we had to translate the areas according to our nomenclature.

Table 1 gives a summary of the studies included in this review. For each study, we describe which imaging modality was used, which experimental design was used and how many subjects were included. In addition, the table shows whether subject groups were matched based on hearing levels and age. Table 2 gives a summary of reported effects on rCBF or BOLD signal of tinnitus related changes using various experimental paradigms. Each column corresponds to one type of paradigm. The symbols indicate several types of change in rCBF or BOLD signal that may correlate with tinnitus in several brain areas (represented by each row in the table).

3.1. Differences in sound-evoked neural activity as an attribute of tinnitus

Several studies measured sound-evoked activity in subjects with tinnitus and compared these responses to those in subjects without tinnitus. Both noise (either broadband or narrow-band noise) and music have been used as experimental stimuli. All studies on sound-evoked responses mentioned in this section made use of fMRI.

Melcher et al. (2000) examined sound-evoked activation to monaural and binaural noise stimuli. For the inferior colliculus (IC), a percentage signal change was calculated, comparing the sound-evoked response to a silent baseline condition. Compared to controls, lateralized tinnitus subjects showed an abnormal small signal change in the IC contralateral to the tinnitus percept, but not ipsilateral. Melcher et al. (2000) argued that tinnitus corresponds with abnormally elevated neural activity. When an external stimulus was presented, the hemodynamic response reached saturation, resulting in a reduced difference between the two conditions (i.e., sound on vs. sound off). This reduction would explain the low signal change in patients compared to controls.

In an unpublished conference abstract Melcher et al. (2005) put their previous results in a different perspective. In the IC of subjects with tinnitus they now measured an increased sound-evoked response compared to controls. To test the influence of ongoing

background noise, a condition with background noise was included, by means of switching the helium pump back on. This caused a reduced response of the IC in subjects with tinnitus, but not in subjects without tinnitus. So, the background sound produced by the scanner pump, may have led to a saturation of the neural response in subjects with tinnitus in initial experiments (Melcher et al., 2000), explaining the reduced IC activity compared to controls.

In recent work sound-evoked responses were studied using a sparse sampling design (Lanting et al., 2008). Stimuli consisted of monaural dynamic rippled broadband noise stimuli at two intensity levels (40 dB and 70 dB SPL). Responses were measured at the level of the primary and secondary auditory cortex combined and the IC of subjects with unilateral tinnitus and near-normal hearing. These were compared with those of subjects without tinnitus. Results showed increased sound-evoked responses, a reduced response lateralization (i.e. stimuli presented to the contralateral and ipsilateral ear gave roughly the same signal change) and a disturbed intensity level dependency in subjects with tinnitus compared to subjects without tinnitus at the level of the IC.

Smits et al. (2007) used binaurally presented music in a block design and compared responses in subjects with tinnitus to those of subjects without tinnitus. Controls showed a leftward lateralization of the PAC (i.e. a predominant left auditory cortex response to sound stimuli). In subjects with bilateral tinnitus however, the sound-evoked response was symmetrical, while the response was lateralized ipsilateral to the side of perceived tinnitus in the PAC. The same pattern, although not statistically significant, was observed in the medial geniculate body (MGB). Kovacs et al. (2006) showed a similar cortical asymmetry in two subjects with unilateral tinnitus (i.e. a smaller sound-evoked response in the cortex contralateral to the tinnitus). Both studies however, did no match their subject groups on hearing levels (normal hearing controls and subjects with tinnitus with hearing losses up to 100 dB). This lack of hearing-level matched groups may have confounded results of both studies, making it difficult to attribute the findings purely to tinnitus.

Table 2
Effect on rCBF or BOLD signals using various experimental paradigms. Each paradigm shows presumable tinnitus-related changes in rCBF or BOLD signals within subjects (somatosensory modulation, gaze-evoked tinnitus, lidocaine and residual inhibition) or differences in rCBF or BOLD signals between groups of subjects (sound-evoked responses and steady state metabolism). The symbols indicate changes in rCBF or BOLD signals for several brain areas corresponding to the paradigm that was used. The numbers in the table refer to the cited authors as shown in the right column and correspond to the numbers in Table 1.

Area	Paradigm						Reference
	Sound-evoked responses	Somatosensory modulation	Gaze evoked tinnitus	Lidocaine	Residual inhibition	Steady-state metabolism	
Frontal lobe				↓[11-13]		▲[19]	1 Melcher et al. (2000)
Limbic system	⇑[6]			↓[12,15]		▲[19]	2 Melcher et al. (2005)
Auditory association cortex		∝[6]	∝[8]	↓[11-13,15] ∝[14]	↑[20]	▲[18,19] asymmetry[17]	3 Lanting et al. (2008)
Secondary auditory cortex	asymmetry[4,5]			↓[13]			4 Smits et al. (2007)
Primary auditory cortex	asymmetry[4,5] ⇑[6,11]	∝[6,7]		↓[10,13]		▲[18,19] asymmetry[16,17]	5 Kovacs et al. (2006)
Thalamus	asymmetry[4]	∝[6]					6 Lockwood et al. (1998)
Inferior colliculus	⇓[1] ⇑[2,3] asymmetry[4]						7 Cacace et al. (1999a)
Lower brainstem				∝[9]			8 Giraud et al. (1999)
Cerebellum				∝[9]	↓[20]		9 Lockwood et al. (2001)

Legend:

Symbol	Meaning
⇑	Increased response to sound in tinnitus subjects
⇓	Decreased response to sound in tinnitus subjects
↑	Increased rCBF or BOLD corresponding to decreased tinnitus
↓	Decreased rCBF or BOLD corresponding to decreased tinnitus
∝	Increased and decreased rCBF or BOLD corresponding to increased and decreased tinnitus, respectively.
▲	Increased rCBF signal in tinnitus subjects
Asymmetry	Abnormal asymmetry in rCBF or BOLD signal

References:

10 Staffen et al. (1999)
11 Mirz et al. (1999)
12 Mirz et al. (2000a)
13 Andersson et al. (2000)
14 Reyes et al. (2002)
15 Plewnia et al. (2007)
16 Arnold et al. (1996)
17 Wang et al. (2001)
18 Langguth et al. (2006)
19 Shulman et al. (1995)
20 Osaki et al. (2005)

The papers (Melcher et al., 2000, 2005; Lanting et al., 2008) appear to be contradictory at first sight: in contrast to Melcher et al. (2000) who reported decreased responses in the IC of subjects with tinnitus, the other two studies showed increased responses. A methodological difference may account for these differences. While Lanting et al. (2008) applied a sparse imaging protocol, in Melcher et al. (2000) images were acquired continuously with high levels of background noise. Therefore, this latter experiment was performed in a relatively noisy environment and may have caused the IC to respond excessively to the scanner noise. Similarly, the sound of the scanner helium pump may cause significant levels of ambient sound, which may reduce the hemodynamic response to the experimental sound stimuli (Melcher et al., 2005).

Thus, Melcher et al. (2000, 2005) and Lanting et al. (2008) are consistent with the interpretation that the IC of subjects with tinnitus displays a disproportionate response to sound, either ambient or experimentally controlled.

Lanting et al. (2008) did not find a difference in the auditory cortices between subjects with tinnitus and controls. This may be a consequence of that fact that they analyzed the auditory cortices as single ROIs, without making a distinction between primary and association areas within each auditory cortex.

Although these sound-evoked responses seem elevated in subjects with tinnitus, another previously unconsidered factor may also play a role. Hyperacusis which is defined as an abnormal sensitivity to sound, may also lead to increased sound-evoked responses and is often coinciding with hearing loss and tinnitus (Møller, 2006b; Jastreboff and Jastreboff, 2003).

3.2. Somatosensory modulation of tinnitus

A second group of functional imaging experiments on tinnitus makes use of the characteristic ability that a subset of subjects with tinnitus appear to have. This is the ability to modulate their tinnitus by some somatic manipulations. Modulation of tinnitus can be achieved by somatosensory interactions like forceful head and neck muscle contraction (Levine, 1999; Levine et al., 2003, 2008; Abel and Levine, 2004) and oral-facial movements (OFMs) like jaw clenching of jaw protrusion (Chole and Parker, 1992; Rubinstein, 1993; Pinchoff et al., 1998). The effect of these manipulations on the tinnitus may express itself as a loudness change, a change in pitch, or both.

Most studies on somatosensory modulation mentioned here have used PET as the imaging modality whereas only one study

on cutaneous evoked tinnitus used fMRI. Other somatosensory manipulations, like movements of the head and neck are known to modulate tinnitus (Levine et al., 2003) but are mostly incompatible with imaging studies due to motion restrictions.

3.2.1. Oral-facial movements

A subset of subjects with tinnitus, varying from about a third of the patient population (Cacace, 2003) to 85% (Pinchoff et al., 1998), can change the loudness of the perceived tinnitus by OFMs.

Lockwood et al. (1998) used $[H_2^{15}O]$-PET to map brain regions in subjects with the ability to alter the loudness of their unilateral tinnitus, and compared their responses to those of subjects without tinnitus. In the tinnitus subjects, the loudness of the tinnitus was either increased (in two subjects) or decreased (in two subjects) by OFMs (jaw clenching). A change of the tinnitus loudness was accompanied by a corresponding change in rCBF in the left PAC and auditory association cortex (Brodmann area (BA) 41 and 21) contralateral to the ear in which tinnitus was perceived upon oral-facial movements: a reduction of the tinnitus resulted in a decrease in rCBF, and an increase of the tinnitus resulted in an increase of the rCBF. Interestingly, monaural cochlear stimulation evoked a bilateral response in the auditory cortical regions. Thus, the lateralization in response to a monaural sound differed conspicuously from that of monaural tinnitus. Not only cortical areas but also the right thalamus including the MGB showed rCBF changes upon OFMs and loudness changes of the tinnitus.

In addition, the authors noticed in subjects with tinnitus compared to controls an increased sound-evoked rCBF in the left PAC as well as an increased sound-evoked rCBF in the limbic system (left hemisphere hippocampus). Although these results suggest abnormal auditory processing in tinnitus subjects, the differences might have been related to differences in age and hearing levels between the subject groups. The subjects with tinnitus had high-frequency hearing losses varying from 30–70 dB while the control group had normal hearing levels. Recent findings of Shore et al. (2008) showed that in animals somatosensory input to the auditory system may be enhanced after noise-induced hearing loss. This result underlines the importance of matching of subject groups on characteristics other than the tinnitus. It suggests that the differences as reported by Lockwood et al. (1998) might reflect changes due to hearing loss rather than purely tinnitus-related neural changes.

Age differences between groups in general also may lead to differences in measured signals (either CBF or BOLD effect). D'Esposito et al. (2003) point out that normal aging, which involves possible vascular changes, may lead to changes in the measured signals which may confound the results if groups are not properly matched.

The last confounding factor may be attributed to gender differences. Gender differences were found showing differences in the primary auditory cortex between males and females in silent lip reading (Ruytjens et al., 2007a) as well as processing of noise stimuli (Ruytjens et al., 2007b). Subject groups should thus be matched on gender to prevent misinterpretation.

3.2.2. Cutaneous-evoked tinnitus

A rare type of somatosensory interaction in tinnitus is cutaneous-evoked tinnitus (Cacace et al., 1999b). Cacace et al. (1999a) described one subject with tonal tinnitus elicited by stroking a region on the backside of the hand, and another subject with tinnitus elicited by touching the fingertip regions of one hand. The latter subject, also having a moderate severe to severe hearing loss in the left ear while having normal threshold at the right ear, was included in an fMRI experiment. A repetitive finger tapping task, eliciting tinnitus, was used while performing fMRI acquisitions. In addition to somatosensory cortical areas, an area in the PAC contralateral to the hand triggering the tinnitus was activated. A control experiment using the

other hand (which did not elicit tinnitus) was also performed, but no changes in activity of the auditory cortex were found. Apparently, finger tapping with the hand contralateral to the tinnitus specifically modulated neural activity in the PAC that is specifically related to the tinnitus percept. Asymmetrical hearing levels could however be a confounding factor in this study.

3.3. Gaze-evoked tinnitus

In gaze-evoked tinnitus, subjects can change characteristics of their tinnitus by rapidly changing gaze or by lateral gaze. Both forms may occur after posterior fossa surgery for gross total excision of space-occupying lesions (mostly vestibular schwannomas of the cerebellopontine angle), often accompanied with complete unilateral loss of the auditory nerve (Cacace et al., 1994, 1999b; Coad et al., 2001; Baguley et al., 2006). The neural mechanism of this phenomenon remains unknown although complete deafferentation of auditory input seems the most common initiator of gaze-evoked modulation of tinnitus.

Giraud et al. (1999) performed a study in subjects with gaze-evoked tinnitus (following profound hearing loss due to the removal of a large tumor) who reported a change in loudness following gaze manipulations (rapidly changing gaze) in the horizontal plane (left–right) and not in the vertical plane (up–down). By contrasting horizontal gaze with vertical gaze they demonstrated in a $[H_2^{15}O]$-PET design that (changes in) tinnitus corresponded to changes of the rCBF bilaterally in auditory association areas (BA 21, 22) but not in the PAC The absence of PAC involvement (i.e. changes in rCBF corresponding to changes in perception of tinnitus) might be explained by pathways that project directly from the MGB to auditory association areas, providing a bypass of the PAC (Møller et al., 1992; Silbersweig et al., 1998). The activity of the auditory association cortex thus might reflect subcortical processing of aberrant neural signals that modulate the percept of tinnitus. This study did not include a control group, which might have disentangled the complex rCBF changes into components that are similar between the groups (and may be normal responses related to changes in gaze) while the differences between groups could reflect tinnitus related rCBF changes.

Lockwood et al. (2001) investigated gaze-evoked tinnitus in a PET design where horizontal (far) lateral gaze induced a loudness change (increase) and central fixation did not. rCBF changes were compared to those in control subjects without tinnitus. Subjects developed gaze-evoked tinnitus after posterior fossa surgery to remove an acoustic neuroma. This surgery was accompanied with complete unilateral loss of the auditory nerve. Gaze-evoked tinnitus was associated with rCBF changes in the lateral pontine tegmentum – a region including the vestibular and cochlear nuclei (CN). In this area, the measured response in subjects with tinnitus was larger than those in the control subjects. It is however difficult to segregate possible tinnitus related activity from hearing loss, since the groups had different hearing levels (in this study only age and sex were matched). In addition, an area in the cerebellum (vermis) was associated with lateral gaze (i.e. lateral gaze contrasted with central fixation). These areas have been reported to control eye movements like saccades and gaze holding (Glasauer, 2003), supporting the hypothesis that crosstalk between the auditory system and the system controlling eye movement might play a role in gaze-evoked tinnitus.

Thus, based on these two reports, is remains unclear what the underlying mechanism of gaze-evoked tinnitus is and whether there is a simple neural correlate of tinnitus. The auditory brainstem (Lockwood et al., 2001) and especially the auditory association cortex (Giraud et al., 1999) show tinnitus related changes in neural activity.

3.4. Lidocaine as modulator of tinnitus

Lidocaine may cause temporary relief of tinnitus when administered intravenously (Melding et al., 1978; Darlington and Smith, 2007). It is a local anesthetic and anti-arrhythmic agent and has both central and peripheral sites of action. Lidocaine affects various molecular channels and receptors in the auditory system (Trellakis et al., 2007), which may explain its effect on tinnitus.

Several neuroimaging studies reported correlation between local rCBF changes and modulation of tinnitus due to lidocaine. Note, however, that lidocaine has dose-dependent effects on the vascular system. It is associated with vasoconstriction in low dose ranges and vasodilatation in high dose ranges (Johns et al., 1985). The neurovascular coupling relates fractional changes in CBF proportionally to fractional changes in oxygen consumption (Buxton et al., 1997) and hence, BOLD signals. Vasodilatation in turn, induces a larger blood flow and hence, larger CBF values and BOLD signal. Local (intracortical) injection of lidocaine on the other hand causes inhibition of multi unit neural activity as well as a reduction in stimulus driven modulation of neural activity as measured with BOLD fMRI (Rauch et al., 2008) Thus it is important to keep in mind that lidocaine may impose global changes in CBF and BOLD effect when administered systemically (causing a dose-dependent vascular change) while it may reduce rCBF and regional BOLD effects when injected locally.

Staffen et al. (1999) measured rCBF in one subject with chronic tinnitus using single positron emission tomography (SPECT), a technique similar to PET imaging. Regional CBF was determined by inhalation of xenon-133 before and after suppression of tinnitus. Lidocaine was used to suppress tinnitus and caused a decrease of global perfusion and reduced rCBF. Effects were stronger in the right auditory cortex compared to the left auditory cortex, thereby reducing left–right asymmetries (existing prior to the lidocaine administration). This lidocaine-induced change in asymmetry in the auditory cortex was not observed in one subject without tinnitus. Although lidocaine may have induced global changes in perfusion (rather than tinnitus-specific changes) as mentioned by the authors, it cannot directly explain the reduction in left–right asymmetry in the auditory cortex compared to one control subject. This last point may indicate a correlation with tinnitus. Note however that there was no change in global CBF in the control subject indicating that the reported effects might not be reliable.

Lidocaine and masking sounds were used in a PET design showing a reduction in rCBF following lidocaine administration (Mirz et al., 1999). Lidocaine administration induced a reduction in rCBF of the right middle frontal gyrus and auditory association cortex (BA 21) when compared to baseline, regardless of the side of the perceived tinnitus. Masking sound on the tinnitus-affected ear(s) showed a decrease of the PET signal from these regions. In addition, there was an increase of rCBF in the left PAC (BA 41) compared to a baseline condition. The authors concluded that lidocaine and masking sounds affect neural activity at different anatomical locations and might involve different mechanisms. This conclusion was however based on a population of subjects with tinnitus without comparing the results to those measured in a control group. It thus remains questionable if the reported changes are indeed solely tinnitus-related.

Mirz et al. (2000a) later showed that administration of lidocaine resulted in a decrease of rCBF in the superior frontal gyrus, the middle frontal gyrus and associative auditory regions in the right hemisphere, as well as a decrease in parts of the limbic system (amygdala, anterior cingulate gyrus) in the left hemisphere (Morgane and Mokler, 2006). The authors concluded based on these results that, in addition to auditory areas, areas associated with emotion and attention play a role in tinnitus. Again, no subjects without tinnitus were included for comparison.

A case of a subject with bilateral tinnitus (left dominant) was studied with [H$_2$^{15}O]-PET (Andersson et al., 2000). Results not only showed a decrease of rCBF in the left PAC, SAC en AAC, but also a right lateralized decrease in frontal paralimbic areas (BA 47, 49, and 15), following administration of lidocaine. Sound stimulation resulted in bilateral activation of auditory areas. They concluded, based on the changes in auditory areas and paralimbic areas, that tinnitus perception is mediated through auditory attention and emotional processing.

Reyes et al. (2002) showed that rCBF changes occurred in the right auditory association area (BA 21 and 22) after lidocaine administration (accompanied with a change in tinnitus loudness), using a single blind, placebo controlled [H$_2$^{15}O]-PET design. The effects of lidocaine were assessed by subtracting the placebo effects from the lidocaine-induced effects. General effects of lidocaine (assessed by subtracting a rest-condition from the lidocaine condition) were an increase in rCBF of the bilateral basal ganglia, cingulate gyrus and the left thalamus. A decrease was observed in the Rolandic fissure. Interestingly, lidocaine could not only cause relief (four subjects), but also an increase in loudness (four subjects), or no change in loudness (one subject).

In a [H$_2$^{15}O]-PET study, Plewnia et al. (2007) also showed a decreased rCBF in the left AAC after lidocaine administration. In addition, they found a reduced rCBF in the right gyrus angularis (BA 39) and the posterior cingulate gyrus (BA 31) of the limbic system. Only patients with a tinnitus loudness reduction after a bolus injection of lidocaine were included in this study. The auditory association cortex was further used as a target for repetitive transcranial magnetic stimulation (rTMS). A dose-dependent decrease in the tinnitus loudness (as measured using a visual analog scale) was observed, i.e. the longer rTMS was performed, the larger the reduction of the loudness of tinnitus. Whether the influence of lidocaine was solely attributed to tinnitus remains however questionable since no control group was used to assess the global effect of lidocaine.

In summary, most studies indicate involvement of the right auditory association cortex (BA 21, 22 and 38) responding to a lidocaine-induced change in the loudness of the tinnitus (Staffen et al., 1999; Mirz et al., 1999, 2000a; Reyes et al., 2002; Plewnia et al., 2007). Although most studies showed that lidocaine induced a decrease in loudness of the tinnitus (Staffen et al., 1999; Mirz et al., 1999, 2000a; Plewnia et al., 2007) and a corresponding reduction of the rCBF in the auditory association cortex, an increase in loudness was also observed (Reyes et al., 2002). Increase in the loudness of the tinnitus also corresponded to an increase in the rCBF in the auditory association cortex. Notably, several studies report changes of neural activity in the non-auditory areas like the limbic system (amygdala and cingulate gyrus) and paralimbic areas that may correspond to a lidocaine-induced change of the loudness of the tinnitus or may correspond to decrease in perceived annoyance, mediated through lidocaine (Mirz et al., 2000a; Andersson et al., 2000; Plewnia et al., 2007).

With the exception of the study of Reyes et al. (2002), none of the other studies included controls or used a placebo-controlled design to assess global effects of lidocaine. This is a serious issue and might hamper the interpretation of the results. Nevertheless, global effects of lidocaine would presumably have symmetrical effects on CBF values while many studies report changes only in the right auditory association cortex. Whether these changes really correspond to a correlate of tinnitus remains debatable.

3.5. Steady state measurements

Steady state metabolic activity in cortical areas can be assessed using radioactive labeled glucose. This approach makes use of ^{18}F-deoxyglucose (FDG), which can be used in a PET design. Locally enhanced brain activity may lead to enhanced glucose uptake and

can be detected by the PET scanner as a local increase of radioactive decay. Due to the relatively long half-life time of ^{18}F (110 min), measurements within one subject using different experimental conditions is not feasible. Rather, only differences between groups can be measured excluding the direct need for manipulating the perceptual characteristics of tinnitus.

Arnold et al. (1996) were the first to make use of FDG-PET to detect changes in metabolic activity and compared measurements of subjects with tinnitus with those of subjects without tinnitus. Results showed a stronger asymmetry in the auditory cortex activity in subjects with tinnitus compared to subjects without tinnitus. Nine subjects with tinnitus showed larger metabolic activity in the left PAC whereas one showed larger activity in the right PAC. These asymmetries might also be due to the tinnitus location (6 left, 2 right, and 2 centrally) and the possible asymmetry in hearing-loss of the tinnitus subjects, making it difficult to attribute asymmetries in metabolic activity with respect to tinnitus.

Wang et al. (2001) repeated this measurement and calculated a symmetry index for the auditory cortex for each subject. Results showed that glucose metabolism in the auditory cortex of subjects with tinnitus was asymmetric between the left and right auditory cortices, with that of the left being higher than that of the right. Note that this was independent of the localization of the perceived tinnitus (4 left, 4 right and 3 centrally). It is not clear whether both groups had a matching degree of hearing loss and whether this was symmetrical. The asymmetry-indices of subjects with tinnitus were significantly higher than those of the control group and in close agreement with Arnold et al. (1996).

Langguth et al. (2006) found asymmetrical activity in the PAC of subjects with tinnitus (17 lateralized to the left and 3 to the right). This was not correlated with the tinnitus location (9 left, 7 right, and 4 centrally). Patients had no to moderately severe, symmetrical hearing loss. No control group was used, making it hard to attribute findings to tinnitus, since cortical activity is not always entirely symmetrical. Also, Langguth et al. (2006) found a correlation between the reduction of tinnitus by rTMS focused at the temporal lobe with the increased rCBF, and the corresponding PET signal strength. This suggests that rTMS can specifically suppress neural activity that is related to the tinnitus percept.

In addition to these FDG-PET studies, Shulman et al. (1995) used SPECT imaging of the brain with technetium-99 m labeling (Tc-HMPAO). In two subjects, significant regional abnormalities in cerebral perfusion bilateral of temporal, frontal, parietal, hippocampal and amygdala regions were demonstrated as compared with normative technetium-SPECT of brain data. No control group was used. Chronologically, this is one of the first imaging results to link the limbic system to tinnitus.

In summary, most studies using steady state measurements report an increased asymmetry in metabolic activity between the left and right PAC in subjects with tinnitus (Arnold et al., 1996; Wang et al., 2001; Langguth et al., 2006). The left PAC shows in almost all cases an increase in metabolic activity as compared to right side (but not all, see cf. Langguth et al. (2006)) suggesting that the asymmetry is related to the tinnitus. Interestingly, this seems not to be dependent on the lateralization of the tinnitus. In addition, steady state measurements show functional changes in other areas like the limbic system in tinnitus (Shulman et al., 1995).

3.6. Residual inhibition

Residual inhibition is a transient suppression of tinnitus after auditory stimulation (Terry et al., 1983; Roberts, 2007). Osaki et al. (2005) made use of this phenomenon and studied three subjects who experienced bilateral tinnitus that was suppressed while their cochlear implant was turned on. After 5–10 min of use of the cochlear implant, residual inhibition was achieved that lasted for

5–10 min. During residual inhibition, the auditory association cortex (BA 21 and 38) showed an increase in rCBF. In contrast, when tinnitus re-emerged, an increase in rCBF in the right cerebellum was observed. rCBF changes in these subjects were compared with those of six subjects with a cochlear implant but without tinnitus. In these subjects, no changes were observed. Thus, residual inhibition of tinnitus was associated with in change in neural activity in the auditory association cortex and cerebellum.

4. Discussion

It is obvious that tinnitus, like any other percept, must be related to some pattern of neural activity in the central nervous system. It seems logical to assume that in tinnitus the pathological activity specifically involves one or more auditory brain areas. The neuroimaging literature reviewed here is generally consistent with this view, although a comprehensive view of the neural activity that underlies tinnitus is still lacking.

Tinnitus is often associated with changes in spontaneous neural activity in the auditory pathway (Kaltenbach, 2000; Eggermont, 2007b). One of the proposed changes is a change in the spontaneous firing rates (SFRs) of auditory neurons that may be responsible for tinnitus. Since an increased (stimulus-driven) firing rate in auditory neurons typically corresponds to the presence of sound source, an increased spontaneous firing rate could also lead to an auditory percept, i.e. tinnitus.

Alternatively, the temporal pattern of spontaneous neural activity could change by e.g. increased synchrony of activity across auditory neurons (Seki and Eggermont, 2003; Eggermont, 2007b). In general, an increased firing rate or increased synchrony of neural activity could be generated by an external acoustical source. Hence, changes in neural synchrony may also be perceived as tinnitus.

The third candidate in the triad of changes that may underlie tinnitus is a reorganization of the tonotopic map in auditory neurons in the central auditory system. Although such changes themselves may not directly correspond to tinnitus, they may contribute to abnormal neural activity. For example, cortical reorganization may lead to the over-representation of frequencies at the edge of a peripheral hearing loss (Rajan et al., 1998; Eggermont, 2006). In other words, eighth-nerve or lower-brainstem neurons that are tuned to an edge frequency could be excessively projected to a region of the auditory cortex.

The neuroimaging modalities discussed in this review (PET and fMRI) are expected to be sensitive to change in overall neuronal activity and additionally may reveal changes in the cortical tonotopic maps if a suitable paradigm is used (Talavage et al., 2004). Hence, these techniques may possibly not identify all changes in neural activity that may relate to tinnitus. Specifically, fMRI and PET will not be able to identify changes in the timing of neural activity at a timescale smaller than about 2 s. Note that this represents a higher temporal resolution than a common TR of 10 s in auditory fMRI Hall et al. (1999) would suggest. This resolution can be obtained by adding jitter to the onset of a stimulus condition, hereby changing the relative timing of the onset of a condition within a fixed TR.

Thus, changes in synchronous neural activity, as suggested by Seki and Eggermont (2003) and Eggermont (2007b) may not be apparent in fMRI or PET data. Nevertheless, some of the neuroimaging results, assessing changes in the magnitude of activity, are very suggestive when interpreted in conjunction with results from animal studies. Table 2 shows the effects on rCBF or BOLD signal of tinnitus related changes using various experimental paradigms.

Below, we discuss the results for the various brain areas and, where possible, compare these to results from animal models of tinnitus. For reasons of clarity, the discussion is organized by brain

area. However, obviously the neural activity in any brain area is not independent of that in other parts of the brain. For example, the neural activity in inferior colliculus in the brainstem will be determined by inherent collicular mechanisms, but also by input from the lower brainstem, the thalamus and the cortex. So, a particular change that is associated with tinnitus would not necessarily reflect a specific role of the inferior colliculus in tinnitus. The change may simply reflect abnormal function of connected brain areas. Since the connectivity analysis of the central auditory system has only applied in a few cases (Goncalves et al., 2001; Langers et al., 2005; Upadhyay et al., 2008), all of which are not related to tinnitus, a discussion on the functional connectivity of connected auditory brain areas is not really possible in relation to tinnitus. Therefore, a discussion of neuroimaging results on a per-brain-area basis seems to be appropriate.

4.1. Lower brainstem

In humans, exposure to loud sounds may produce hearing loss and tinnitus. Several studies in animals show that hearing loss caused by exposure to loud sounds results in an increase of neural activity in the CN. These changes are present in the dorsal CN (Kaltenbach et al., 1998, 2000; Zhang et al., 2006), and in the ventral CN (Brozoski et al., 2007). Enhanced SFRs in the CN presumably result in enhanced activity in other auditory brain areas including the cortex, which may then cause tinnitus.

Imaging studies in humans only occasionally describe details of the lower brainstem. This may be due to a number of factors. The first factor is the poor spatial resolution (which is about 2–5 mm, depending on the technique that is used) compared to the nuclei that is imaged. This results in only 3–4 voxels corresponding to the CN (Hawley et al., 2005). A second factor is the poor signal-to-noise ratio that is typically obtained when imaging the lower brainstem. At present, there is no imaging study that shows enhanced spontaneous activity in the CN in tinnitus patients, which would correspond to enhanced neural activity described in animals.

The CN may well be the nexus of somatosensory modulation of tinnitus. In guinea pigs, both the ventral and dorsal CN receive somatosensory input via the trigeminal ganglion (Shore et al., 2008; Dehmel et al., 2008). Another source of multisensory interaction involves projections of the dorsal column nuclei and to the CN (Itoh et al., 1987). These anatomic and functional connections between the somatosensory and the central auditory system may underlie the influence of somatic modulation on tinnitus that is frequently described by patients with tinnitus (Levine, 1999; Levine et al., 2003). Somatosensory-based treatment modalities might be useful for a tinnitus subgroup that exhibit somatosensory modulation (Levine et al., 2007).

Lockwood et al. (2001) showed a change in rCBF in the CN accompanying the perceptual change of tinnitus by lateral gaze. An increase of tinnitus loudness was correlated to an increase of the rCBF in the CN. Currently, this is the only neuroimaging study that describes results in the CN of tinnitus patients.

So, at present, one neuroimaging study of modulation of tinnitus by gaze indirectly suggests changes of neural activity of the CN in tinnitus, although it is not clear to what extent the observed effects are directly related to tinnitus or that the effects are related to differences in hearing loss between groups. Neuroimaging evidence for enhanced spontaneous activity of the CN in tinnitus is currently lacking.

4.2. Inferior colliculus

For the inferior colliculus (IC), both animal data and human fMRI provide some insight in the neural mechanisms related to tinnitus. Chinchillas with noise trauma and behavioral evidence of tinnitus, show increased spontaneous activity (SFRs) and enhanced sound-evoked responses in the IC (Salvi et al., 1990, 2000; Wang et al., 2002; Brozoski et al., 2007). The enhanced neural activity, again, may correspond to tinnitus, reflecting reduced effectiveness of inhibitory neural circuits, which has also been suggested in tinnitus (Eggermont and Oct, 2005; Møller, 2006a).

The human IC is a structure that can be easily identified on an MR image. Its neural response is typically well detectable in auditory fMRI experiments using a sparse sampling design (Langers et al., 2005). The small size of the IC at standard imaging resolution does not allow for the identification of functional substructures. Rather, the activity of the IC is usually expressed as a single region-of-interest response. The IC is typically not identifiable in functional PET studies, presumably because of its small size.

While current functional MRI paradigms cannot identify changes in SFRs, an abnormal sound-evoked response has been found in tinnitus patients. Although one initial study reported a different result (Melcher et al., 2000), two recent studies from independent groups (Melcher et al., 2005; Lanting et al., 2008) show an increased sound-evoked response in subjects with tinnitus with nearly normal hearing. In addition, a disturbed lateralization of activity was observed (Smits et al., 2007; Kovacs et al., 2006), although in these studies the subjects groups had no matching hearing levels (normal hearing controls and subjects with tinnitus with hearing losses up to 100 dB). This may have confounded results, making it difficult to attribute the findings to tinnitus.

Thus, the animal and human data suggest that enhanced sound-evoked responses of the IC are characteristics of both tinnitus and hearing loss. This abnormal sound-evoked activity may be caused by pathology that is inherent to the IC. Alternatively, it could result from abnormal neural input from a lower or a higher part of the auditory pathway. It is currently unclear whether the enhanced activity is at all related to tinnitus. It might also reflect hyperacusis, a common complaint of tinnitus patients, which is also believed to be related to enhanced activity of the central auditory system (Formby et al., 2003; Møller, 2006b). Nevertheless, it is possible that the abnormal IC responses observed in tinnitus patients are somehow related to the tinnitus percept. The difference observed between tinnitus patients and controls, both with near-normal hearing, is an indication that central auditory processing in the brain stem is abnormal in patients with tinnitus.

4.3. Thalamus

The extensive bottom–up (afferent) and top–down (efferent) connections between the medial geniculate body of the thalamus (MGB) and the auditory cortex suggest a key role of the thalamus in auditory perception. Connection between the cortex and the thalamus are believed to contribute to the steady-state brain rhythms that can be observed in EEG and MEG signals. These brain rhythms seem abnormal in patients with tinnitus (Weisz et al., 2005b,a; Llinas et al., 2005) and may indicate pathology in the cortico-thalamic loops although subjects were not always matched on their hearing levels in these studies which may act as a confound. Salicilate-induced changes in spontaneous activity (SFR) in the MGB (Basta et al., 2008) underline the role the MGB may play in tinnitus.

Somatosensory modulation of tinnitus by oral-facial movements (OFMs) showed a correlation between rCBF changes in the right MGB and tinnitus loudness (Lockwood et al., 1998) and could very well be mediated through pathways projecting to nuclei of the thalamus (Møller et al., 1992). Interestingly, recent findings of Shore et al. (2008) showed that in animals somatosensory input to the auditory system may be enhanced after noise-induced hearing loss. Thus, the effects as reported by Lockwood et al. (1998)

might reflect changes due to hearing loss rather than tinnitus. The role of the MGB in tinnitus is thus marginally demonstrated.

4.4. Primary auditory cortex

The auditory cortex is important in sound perception, although the auditory system exhibits some capacity to, for example, discriminate frequencies after bilateral ablation of cortical auditory areas (Goldberg and Neff, 1961). Nevertheless, the human PAC (often described as BA41) invariably responds to acoustic stimulation of the ear (Elliott, 1994; Johnsrude et al., 2002; Binder et al., 1994; Belin et al., 1999). Moreover, the PAC is associated with auditory hallucinations in patients with schizophrenia (Dierks et al., 1999). Consequently, it seems very likely to assume that neural activity in the PAC plays some role in all human sound perception, including tinnitus. Hence, tinnitus is almost certainly related to some aspect of neural activity in the PAC.

In cats, the SFRs of neurons in the PAC was increased after noise trauma (Noreña and Eggermont, 2003). Also, an increase in synchrony of neural activity was observed (Seki and Eggermont, 2003). Additional neural plasticity was observed following acoustic (pure-tone) trauma, which resulted in a change in the cortical tonotopic map (Komiya and Eggermont, 2000; Eggermont, 2006). Recently, salicylate-induced tinnitus in rats was found to increase FDG activity in the auditory cortex using a micro PET imaging technique (Paul et al., 2009). Together, these data show that induced hearing loss causes changes in both the level of activity and the synchrony between neurons of the PAC.

If tinnitus in humans also corresponds to a change in activity in PAC, one would expect this to lead to measurable effects in neuroimaging studies. The positive correlation between tinnitus loudness and rCBF, that was shown in experiments where tinnitus was modulated by somatosensory excitation (Lockwood et al., 1998; Cacace et al., 1999a,b) or lidocaine (Andersson et al., 2000) do suggest a direct coupling between tinnitus and PAC activity. In addition, some steady state metabolism studies showed an increase of rCBF (Shulman et al., 1995) or an increased asymmetry (Arnold et al., 1996; Wang et al., 2001; Langguth et al., 2006) in the PAC of subjects with tinnitus, as compared to non-tinnitus subjects. Similar asymmetries between both hemispheres have also been reported using fMRI (Smits et al., 2007; Kovacs et al., 2006).

One study however showed no difference between sound-evoked responses of subject with tinnitus and those of controls in the auditory cortex (Lanting et al., 2008). This demonstrates that either, there is no change in neural activity, that any tinnitus-related changes are not measurable with fMRI, or the slight age and/or hearing differences between tinnitus and control subjects prevented any difference from being seen. Note that in this study a large ROI was taken combining both the PAC and secondary auditory areas. The measured responses thus have contributions from both areas rather than from the PAC exclusively. In addition to this, there is one study on gaze-evoked tinnitus showing the absence of PAC activity related to tinnitus (Giraud et al., 1999). Instead, the auditory association cortex did show a tinnitus related difference in activity.

Many of the studies described have some serious limitations making it difficult to segregate possible tinnitus-related activity from other confounds like the lack of a control group or a control group that was improperly matched to the tinnitus subjects with respect to e.g. hearing levels, age and gender. Nevertheless, the body of results (except two) strongly suggests that tinnitus may be associated with increased neural activity in the PAC.

4.5. Secondary auditory cortex and auditory association cortex

Both animal and human studies suggest an involvement of the secondary auditory cortex in tinnitus. In cats, administration of the salicylate and quinine (known to induce tinnitus in humans) was reported to result in an increase in the spontaneous firing rate in the secondary auditory cortex (Eggermont and Kenmochi, 1998).

Some of the human imaging studies, mentioned in the previous section concerning the PAC, also showed that the secondary auditory cortex (Andersson et al., 2000) or the auditory association cortex (Lockwood et al., 1998; Langguth et al., 2006; Shulman et al., 1995; Wang et al., 2001) were related to tinnitus.

Interestingly, one study on gaze-evoked tinnitus showed responses in the auditory association cortex, but not in the PAC (Giraud et al., 1999). The apparent bypass of the PAC could also be observed in other studies that used modulation of the perceptual characteristics of tinnitus like lidocaine (Mirz et al., 1999, 2000a; Reyes et al., 2002) and residual inhibition (Osaki et al., 2005). This bypass suggests involvement of the non-classical auditory pathway (Møller et al., 1992), which directly projects from the MGB to the auditory association cortex. Of course, the fact that no responses in the PAC were measured, does not necessarily mean that the PAC was uninvolved with tinnitus.

In summary, some studies on modulation of tinnitus by lidocaine, lateral gaze or residual inhibition, show association with the perceptual changes of the secondary auditory cortex but not the PAC. On the other hand, there are studies described here that actually find association of the primary, secondary auditory cortex and auditory association cortex with tinnitus. Thus, many studies show that the secondary auditory cortex and the auditory association cortex behave differently in patients with tinnitus while this behavior in the PAC is not always clearly observed.

4.6. Limbic system and the frontal lobe

The limbic system is participating in many aspects of life involving and regulating motivation, mood, and emotion (Dalgleish, 2004). It consists of many subsystems (Morgane and Mokler, 2006) of which the hippocampus, the amygdaloid complex, the cingulate gyrus and the prefrontal cortex are important parts. Typical complaints attached to tinnitus, such as problems with sleep, anxiety, depression, and emotions such as fear, indicate the association of the limbic system with tinnitus (Jastreboff, 1990). Several cognitive therapies for tinnitus presumably affect the interaction between frontal, limbic and auditory brain areas. By reducing or altering the emotional content of the tinnitus percept by habituation (Jastreboff and Jastreboff, 2003; Jastreboff, 2007), many subjects with tinnitus can find relief from their complaints. With this approach the percept of tinnitus may not be altered, but its emotional attributes are.

In humans, the connections of the limbic system with tinnitus have not often been shown in imaging results. The hippocampus showed increased rCBF in steady state measurements in subjects with tinnitus (Shulman et al., 1995) and showed a sound-evoked response whereas it did not in controls (Lockwood et al., 1998).

A role for the amygdala in tinnitus was also suggested in steady state measurements in two subjects with tinnitus (Shulman et al., 1995). The use of lidocaine has revealed that the decrease of loudness in subjects with tinnitus was accompanied by a decrease in rCBF in the left amygdala and anterior cingulate gyrus (Mirz et al., 2000a). A lidocaine-induced decrease of rCBF was also observed at the posterior cingulate gyrus (Plewnia et al., 2007). Not many studies did actually include a proper control group or made use of placebo-controlled design (e.g. lidocaine vs. placebo), thus limiting the interpretation of these studies. Only one study mentioned global effects of lidocaine and shows increased rCBF of the pons, midbrain and left and right basal ganglia as well as cingulate gyrus in response to lidocaine administration (Reyes et al., 2002).

In addition to the limbic system, also the frontal lobe shows also involvement in tinnitus. Lobotomy of the frontal lobe may decrease

the annoyance of tinnitus but leaves the perceived loudness unchanged (Beard, 1965). Apparently, the frontal lobe is associated with the emotional response to tinnitus. Involvement of the right middle frontal gyrus was observed as a lidocaine induced rCBF decrease accompanied by a reduction in tinnitus loudness (Mirz et al., 1999).

In summary, several studies that show association of the limbic system and frontal lobe with tinnitus that are based on the modulation of tinnitus by lidocaine. These results could be based on a global effect of lidocaine on rCBF (Reyes et al., 2002). Nevertheless, results are consistent across studies and suggest that the limbic system and the frontal lobe are associated with tinnitus. Yet, the mechanisms behind these brain systems and the influence on tinnitus remain unknown.

4.7. Cerebellum

The cerebellum is involved primarily in planning of motor actions, motor control, and motor learning. In addition, it was proposed that the cerebellum might also be associated with higher-order functions (Schmahmann, 1991). This view is not without controversy (Glickstein and Doron, 2008), as most higher-order processes co-occur with eye movement control (Glasauer, 2003). Experimental paradigms that involve a higher-order task often involve eye-movements. Thus, the cerebellum activity that is associated with a task may in fact reflect the eye movement motor control, rather that higher-order processing related to the task.

Nevertheless, auditory sensory processing in the cerebellum has been reported. Fifteen studies reporting neural correlates of passive and active listening were summarized in a meta-analysis (Petacchi et al., 2005) and a general role of the cerebellum in auditory processing was found. Indeed, from an animal study in cats, anatomical connections between the CN and parts of the cerebellum were shown to exist (Huang et al., 1982) forming an anatomical basis for auditory sensory input into the cerebellum.

Evidence of the participation of the cerebellum in tinnitus is sparse. In rats with noise-induced tinnitus, elevated neural activity was observed in the paraflocculus of the cerebellum (Brozoski et al., 2007). In humans, this area has also been shown to be active in subjects without tinnitus in response to sine-wave tones (Lockwood et al., 1999).

The association of the cerebellum with tinnitus has been discussed in only a few studies. In addition to the vermis, involved in integrating head and eye position in combination with vestibular signals (Lockwood et al., 2001), the right cerebellum was also reported in tinnitus and showed a decreased rCBF during residual inhibition (Osaki et al., 2005). Although not directly related to tinnitus, aversive sounds mimicking tinnitus presented to subjects without tinnitus also showed rCBF changes in the cerebellum (Mirz et al., 2000b).

All evidence put together, the association of the cerebellum with tinnitus is not substantially supported by the current neuroimaging studies.

5. Conclusion

A number of fMRI and PET imaging studies aimed to identify the neural correlates of tinnitus. Both imaging modalities depend on the hemodynamic response to neural activity. They may identify changes in local neural activity that result from induced modulation of tinnitus and, in some cases, may identify abnormal steady-state activity associated with tinnitus.

PET and fMRI have a limited spatial (∼mm) and temporal (∼s) resolution. This limits the use of these methods to the investigation of the rather slow hemodynamic responses that can be identified

in brain areas, summarizing responses of a large number of neurons. In addition, these methods only measure the strength of activity. Subtle changes in e.g. neural synchrony that have also been suggested to relate to tinnitus (Eggermont, 2007a) presumably remain unnoticed when the brain is studied with PET or fMRI.

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

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

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