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Corresponding Author: Dr. Peyman Adjamian, Ph.D

Corresponding Author's Institution:

First Author: Peyman Adjamian

Order of Authors: Peyman Adjamian; Magdalena Sereda; Deborah A Hall

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The mechanisms of tinnitus: Perspectives from human functional neuroimaging

Peyman Adjamian [a] : peyman@ihr.mrc.ac.uk

Magdalena Sereda [a] : Magdalena@ihr.mrc.ac.uk

Deborah A. Hall [a,b] : d.hall@ihr.mrc.ac.uk

[a] MRC Institute of Hearing Research

University Park

Nottingham, UK

NG7 2RD

[b] National Biomedical Research Unit in Hearing

Floor 14, Tower Building

University of Nottingham

University Park

Nottingham, UK

NG7 2RD

Corresponding author: Peyman Adjamian.

Telephone (with country and area code): +44 (0) 115 9223431

Fax numbers (with country and area code): +44 (0) 115 9518503

Email: peyman@ihr.mrc.ac.uk

Abstract

In this review, we highlight the contribution of advances in human neuroimaging to the current understanding of central mechanisms underpinning tinnitus and explain how interpretations of neuroimaging data have been guided by animal models. The primary motivation for studying the neural subtrates of tinnitus in humans has been to demonstrate objectively its representation in the central auditory system and to develop a better understanding of its diverse pathophysiology and of the functional interplay between sensory, cognitive and affective systems. The ultimate goal of neuroimaging is to identify subtypes of tinnitus in order to better inform treatment strategies. The three neural mechanisms considered in this review may provide a basis for TI classification. While human neuroimaging evidence strongly implicates the central auditory system and emotional centres in TI, evidence for the precise contribution from the three mechanisms is unclear because the data are somewhat inconsistent. We consider a number of methodological issues limiting the field of human neuroimaging and recommend approaches to overcome potential inconsistency in results arising from poorly matched participants, lack of appropriate controls and low statistical power.

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Introduction

Tinnitus is the conscious perception of sound that cannot be attributed to an external sound source. It is sometimes referred to as 'phantom' auditory experience. The percept takes a variety of forms including tonal, hissing, ringing, whistling or 'cricket-like' sound. Tinnitus is prevalent in the general population, with approximately 10-15% of people experiencing it in some form. For about 20% of people experiencing tinnitus, it is sufficiently bothersome to seek treatment from their doctor or hearing specialist (Jastreboff and Hazell, 1998; Davis and El Rafaie, 2000; Andersson et al., 2005).

Two broad categories of tinnitus have been defined. 'Objective tinnitus' refers to the rare number of cases in which the sound source can be identified and may be audible to others. For example, abnormal blood flow pulsations in vessels adjacent to the middle-ear bones can cause the stapes to vibrate against the oval window. Objective tinnitus has also been associated with abnormal rhythmic muscle contractions that occur in number of disorders like aneurysm and palatal myoclonus (Henry et al. 2005). In contrast, 'subjective tinnitus' refers to the more common form in which the source of the auditory sensation cannot be clearly identified. In this review, we are primarily concerned with chronic subjective tinnitus and this problem will henceforth be referred to simply as 'tinnitus' (TI). Although certain common trends are found across the patient population, TI can have many different underlying causes. In particular, TI often co-occurs with sensorineural hearing loss (Hoffman and Reed, 2004) and so its prevalence increases with age (Newall et al., 2001). For example, in a survey of 555 patients attending a TI clinic, 42% of those also reported presbycusis (Nicolas-Puel et al., 2006). Numerous studies report an association between the TI pitch and the region of the hearing loss (Noreña et al., 2002, Konig et al., 2006; Roberts et al., 2006; 2008) (Figure 1). However, TI is not restricted to those

with age-related hearing loss. In a survey of over 2,000 TI patients, Henry et al. (2005) reported that prolonged noise exposure and noise trauma were an associating factor for the majority of cases (22%), followed by head and neck injury (17%), infections and neck illness (10%) and drugs and other medical conditions (13%). The rest could not identify any specific known event associated with their TI onset.

*** Figure 1 here ***

TI can be either a transient experience or a persistent chronic disorder (Davis and El Rafaie, 2000). For example, in the National Study of Hearing, the criterion for TI was defined as a percept that lasted at least 5 minutes (Davis, 1995). However, the severity of TI varies within and between patients. The perceptual characteristics of TI include its temporal duration, spatial lateralisation, loudness, pitch and sensitivity to residual inhibition. Henry and Meikle (2000) provide a comprehensive review of research in the characteristics of TI that can be studied using psychoacoustic techniques. A complex interplay of psychological, psychosocial, environmental factors and personality traits also contribute to the perception of TI and its effect on an individual's quality of life (House 1981; Henry and Wilson, 2001).

It is now accepted that central mechanisms play an important role in TI aetiology. While peripheral abnormalities in the cochlea may trigger TI they are not necessary for its maintenance because in many cases it persists even after transection of the auditory nerve (House and Brackmann, 1981; Pulec, 1984). This review provides a critical overview of human functional neuroimaging studies that have not only been highly influential in providing the evidence for the importance of central processing to TI sensations but have also attempted to identify putative models for the underlying neural mechanisms, with guidance from animal electrophysiology.

Guiding principles from animal studies

Perceptual and psychological measures of TI are insufficient to identify the neural mechanisms involved and to distinguish between potential subtypes of the disorder. Most of our current understanding about the neural mechanisms originates from research using invasive animal recordings of single and multi-units in the auditory system, both *in vivo* and *in vitro*. These studies have been highly informative for identifying neurophysiological correlates of TI by revealing the direct consequences of ototoxic drugs and noise trauma on the structure and function of the auditory system. The interpretation of human neuroimaging data is strongly guided by such findings, although at least four caveats limit the direct linkage between the two different types of measures. When reading the neuroimaging literature, one must remain vigilant for author biases towards highlighting positive associations between the observed results and previously reported electrophysiological data in order to propose some plausible model of the neural underpinnings of TI, without drawing attention to the potential limitations of doing so.

First, one of the most common ways to induce TI in an animal is by the application of ototoxic drugs such as salycilate (aspirin), quinine, kanamycin and furosemide. Ototoxic drugs are well known to cause hearing loss and TI, although few human cases have the same aetiology. For example, Henry et al. (2005) reported that drugs and other medical conditions accounted for only 7% of TI in the clinic. Furthermore, high doses of the drug are toxic and so their damaging effects probably extend beyond the cochlea. Since pharmacological agents may induce specific patterns of abnormal activity in the central auditory system they are not necessarily a good model for the more common forms of TI. When noise trauma is used to induce TI, its effects are much more variable across individual animals (Heffner and Harrington, 2002). Thus, while noise

trauma may provide a more appropriate model for TI in humans, its use in the laboratory is not so popular.

Second, the complex effect of anaesthesia on central auditory function is not fully understood. Depending on the dosage, common anaesthetics like ketamine and pentobarbital can differentially decrease spontaneous activity of neurons (Ritz and Brownell, 1982; Kuwada et al., 1989; Zurita et al., 1994), decrease or increase the size of burst discharges (Zurita et al., 1994), change the frequency tuning of neurons (Gaese and Ostwald, 2001), induce changes of amplitude and latency of brainstem auditory responses (Church and Gritzke, 1987; Church and Shucard, 1987; Astl et al., 1996), reduce the inhibitory subregions (Evans and Nelson, 1973; Anderson and Young, 2004), as well as change the tonotopic organisation in auditory structures (Imig and Morel, 1985). Moreover, anaesthetic effects are not constant. They can vary from one neuron to the next and tend to be more pronounced in the central than in the peripheral auditory system. Therefore, neural activity that is interpreted as the correlate of TI may differ between anaesthetised and awake states. Moreover, both anaesthesia and ototoxic drugs modify neural activity within the central auditory system (e.g. Kenmochi and Eggermont, 1997), adding further complexity to the interpretation of abnormal neural activity. Thus, abnormal patterns of activity observed during the anaestetised state may not be directly applicable to the awake state (either animals or humans).

Third, despite sophisticated behavioural methods to evaluate the presence and severity of TI in animals (Lobarinas et al., 2004) no measures are directly equivalent to those obtained in humans. Methods in the animal laboratory include gap pre-pulse inhibition of acoustic startle (Yang et al., 2007), schedule-induced polidypsia avoidance conditioning (Lobarinas et al., 2004; Yang et al., 2007), active avoidance (Guitton et al., 2003) and conditioned suppression and

avoidance (Jastreboff and Sasaki, 1994). While some conditioning paradigms can provide estimates of pitch and loudness (Jastreboff and Sasaki, 1994), a complete characterisation of the perceptual and psychological attributes of TI cannot be established in laboratory animals. One clear advantage of working with people is their ability to introspect and report on their own perceptions and feelings.

Finally, while animal studies measure TI-related neural activity on a microscopic level (single or multiple neurons), human neuroimaging measures the same events on a macroscopic level (neural populations). Of all the non-invasive neuroimaging methods, electroencephalography (EEG) and magnetoencephalography (MEG) are the most directly related to electrical activity of the neural population. Such signals represent the sum of local synaptic voltages and this corresponds to the low-pass filtered range (cut off < 200 Hz) of the extracellular field potential, namely the local field potential (LFP) (Logothetis et al., 2001). Although the LFP represents the input to and intracortical activity within a neural population, it is not necessarily correlated with spike output because LFPs are not necessarily supra-threshold (Heeger and Rees, 2002). Spiking activity measured in animal studies corresponds to the high-pass component (cut off >300 Hz) of the extracellular field potential and represents the output of the neural population. In most circumstances, LFPs are highly correlated with local average firing rates, but this is not always the case. Thus, neural phenomena observed in the animal model may not always be detectable in humans using non-invasive neuroimaging methods.

The neural mechanisms of TI

The prevailing opinion is that TI is a perceptual consequence of altered patterns of intrinsic neural activity generated along the central auditory pathway following damage to

peripheral auditory structures (Eggermont and Roberts, 2004). While the loss of afferent input to the central auditory system can initiate TI, thereafter, central mechanisms play an important role in maintaining it. The challenge is to discover the correspondence between the different aetiologies of TI, their perceptual characteristics and patterns of abnormal brain activity. Interpretive leverage may be gained by closely linking individual audiological, perceptual and psychological profiles to the observed patterns of TI-related brain activity in order to distinguish one type of TI from another. However, while some neuroimaging studies do report such information (Melcher et al., 2000; Lockwood et al., 2001; Diesch et al., 2004), it has never been carried out with this primary aim in mind.

Invasive electrophysiological recordings in the mammalian auditory system have typically identified three different classes of abnormal activity that follow sensory deafferentation and may also provide an objective marker for TI when it is associated with hearing loss. These three classes are; i) changes in the spontaneous stochastic neural firing rate during the resting state, ii) changes in the temporal firing pattern of otherwise stochastic spontaneous activity (both in terms of bursting activity within a neuron and synchronous, oscillatory activity between neurons), and iii) reorganisation of the tonotopic map. Using MEG or EEG, an abnormally elevated response to external sounds (hyperexcitability) has also been shown to co-occur with TI (e.g. Hoke et al., 1989; Noreña et al., 1999; Kadner at al., 2002), but such hyperexcitability has been reported at frequencies unrelated to the dominant TI pitch and a number of studies have failed to replicate these results (Jacobson et al., 1991; Colding-Jorgensen et al., 1992; Attias et al., 1993), suggesting that this abnormal activity is unlikely to underpin the TI percept. The main focus of our review discusses the evidence for the three mechanisms, linking the animal models to current perspectives from human neuroimaging. Although there is a

large body of evidence regarding the functional role of the cochlea, auditory nerve and dorsal cochlear nucleus in TI, we restrict our focus on brain structures that can be reliably measured non-invasively in humans; namely inferior colliculus, auditory thalamus and cortex.

i) Increased spontaneous stochastic firing rate

Guidance from animal electrophysiological studies

Many animal studies have shown evidence for increased spontaneous activity after administration of TI-inducing agents and noise trauma. Given that an external sound stimulus is normally signalled in the auditory system by an increased rate of neural firing, it is plausible that TI is consequence of a pathological increase in the rate of spontaneous random firing which can be erroneously interpreted as sound. Of relevance for human neuroimaging studies, animal models of TI have reported increased spontaneous firing rate in neurons within inferior colliculus (e.g., Jastreboff and Sasaki, 1986; Willott et al., 1988; Chen and Jastreboff, 1995; Manabe et al., 1997; Salvi et al., 2000b), medial geniculate body (e.g., Wallhäuser-Franke, 1997; Wallhäuser-Franke et al., 2003) and auditory cortex (e.g., Ochi and Eggermont, 1996; Kenmochi and Eggermont, 1997; Eggermont and Kenmochi, 1998; Eggermont and Komiya, 2000; Seki and Eggermont, 2003; Noreña and Eggermont, 2003). In inferior colliculus, it has been shown that spontaneous activity changes do not necessarily occur in all of its subdivisions, but are most prominent in the central and external nuclei, in those neurons tuned to high (10-16 kHz) frequencies likely to correspond to the TI pitch in animals (Jastreboff and Sasaki, 1986; Chen and Jastreboff, 1995, Willott et al., 1988). Similarly, within primary auditory cortex (A1), Eggermont and colleagues have reported that TI-inducing drugs tended to increase spontaneous firing rate for neurons tuned to high frequencies and decrease firing rate for neurons tuned to low

frequencies (Kenmochi and Eggermont, 1997; Eggermont and Kenmochi, 1998). After noise trauma, increased spontaneous activity within the area of tonotopic reorganisation has been attributed to a reduction in the proportion of neurons with a low spontaneous firing rate, rather than to an overall rise in firing rate (Eggermont and Komiya, 2000; Noreña and Eggermont, 2003).

The implications of this result for human neuroimaging are worth clarifying. If an abnormal spontaneous stochastic firing rate occurs in only a small part of the tonotopic map, then the change in the population response may be too little to perturb the neuroimaging signal. In fMRI for example, one voxel would typically therefore encompass the entire nucleus of the inferior colliculus because it has a volume of about 0.032 cm^3 (equivalent to the volume of a cube with a 3 mm side). Although frequency specificity within primary auditory fields can in principle be distinguished using fMRI, statistical sensitivity to fine-grained changes would require very careful individual analysis. Thus, at best, human neuroimaging is most likely to be sensitive to gross changes in spontaneous firing involving a spatially extensive population of neurons.

Human neuroimaging studies

Although elevated spontaneous activity related to TI has been demonstrated in animals, there is little direct evidence from humans. Changes in the overall rate of stochastic neural firing are not detectable using EEG or MEG recording methods (Figure 2A) due to the nature of the signals that are measured. For a review of EEG and MEG see Baillet et al. (2001). Both techniques share a common generating source which is the current flow associated with the postsynaptic potentials of apical dendrites of pyramidal cells in the superficial layers of the

cortex (Nunez and Srinivasan, 2006). MEG signals represent the magnetic fields corresponding to the 'primary' electrical activity generated by intracellular currents and are measured on the scalp using special sensors. In contrast, EEG signals represent the 'secondary' electrical potentials on the scalp that are produced by the extracellular currents associated with the intracellular neural activity. To be detected on the scalp, individual synaptic signals must be summed across a local population of approximately 10^4 to 10^5 neurons. The EEG and MEG signals thus reflect the synchronous population response in the millisecond time scale at the macroscopic level. Signal amplitude is determined by the degree of spatial and temporal synchrony between postsynaptic potentials and best temporal summation occurs for those with zero temporal lag (Nunez and Srinivasan, 2006). EEG and MEG are somewhat limited in their spatial localisation because an infinite number of intracranial sources could give rise to the measured pattern of signals at the scalp (the inverse problem). Furthermore, EEG signals are distorted by the electrical conductance of the surrounding tissue, blurring signals over a distributed number of sensors. A specific problem for MEG is that neural sources that are orientated in a perfectly radial orientation to the scalp do not generate a magnetic field and so cannot be detected (but see Hillebrand and Barnes, 2002).

Other neuroimaging methods rely on a different type of generating signal. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) commonly measure blood flow, blood volume, oxygen concentration and glucose metabolism, reflecting local neuronal activity, drug uptake and neurotransmitter release (Lammertsma, 2001). The precise process measured is determined by the choice of radioactive isotope (e.g. ^{18}F, ^{13}N, ^{11}C or ^{15}O) and by the duration of its half life. Various compounds that cross the blood brain barrier and have a short half life are typically used to measure functional activity. For example, ^{15}O is widely

used to measure perfusion. The labelled tracer is injected (as water) or breathed in (as air) and binds to water, circulating in the bloodstream and becoming concentrated in active brain regions (for a review see Herscovitch and Ernst, 2000). As the tracer loses energy over its half life of 2 minutes, it emits radiation signals (gamma rays) that are detected by an array of sensors around the head. The most common tracer for quantifying metabolic activity is ^{18}F-fluorodeoxyglucose (FDG). This compound is phosphorylated by the brain through the same pathway as glucose and has a half life of 110 minutes. For example, Arnold et al. (1996) reported increased resting metabolic activity in primary auditory cortex for a group of 10 out of 11 patients with chronic TI compared to 14 controls. However, a number of methodological issues limit the more widespread use of SPECT and PET. In particular, they have a relatively low temporal and spatial resolution and their invasive nature limits safe dosages, thus yielding individual data with a low signal-to-noise ratio.

While PET can be used to measure absolute brain activity, both PET and functional magnetic resonance imaging (fMRI) are more commonly used to measure the relative differences between two states (such as active listening versus resting). fMRI measures brain activity using an intrinsic signal that is based on the change in blood oxygenation and its effect on the magnetic properties of surrounding tissue. This intrinsic signal is known as the blood oxygenation level dependent (BOLD) response. The use of subtraction-based paradigms poses a problem for measuring TI-related activity because the sensation is either continuous or fluctuates in an uncontrolled manner. Fortunately many patients are able to voluntarily modify their TI, for example by eye gaze or facial movement (Levine, 1999b). In others, the TI level can be modulated in other ways, for example by a noise masker (Mirz et al., 1999; Melcher et al., 2000), by the administration of pharmacological treatments such as lidocaine (Staffen et al., 1999;

Andersson et al., 2000) or by the application of neural stimulation using a TMS coil (de Ridder et al., 2004; 2005). TI-related activity can be identified by taking advantage of these manipulations to create experimental paradigms that lend themselves to statistical subtraction. This approach assumes that continuous TI influences the way in which the central auditory system responds to external sounds or that manipulations to modulate the TI percept correlate with changes in underlying neural activity. Conveniently these approaches enable TI patients to act as their own comparison, providing further statistical control to across-group comparisons. For any conclusion to have some diagnostic or predictive validity, sufficient statistical power is required to support the inference that the mean effect over the population is significantly greater than under the null hypothesis. This typically requires a random-effect analysis in which the subject-to-subject response variability can be reliably estimated and for this the dataset should ideally include more than 20 subjects (Thirion et al., 2007). A majority of functional neuroimaging studies fail to reach such numbers and to illustrate this point, we highlight sample size throughout our review.

**** Figure 2 here****

Suppression of TI using noise maskers and residual inhibition The effect of masking noise on suppressing TI-related activity has been investigated within the inferior colliculus using fMRI (Melcher et al., 2000) and within auditory cortex using PET (Mirz et al., 1999). Mirz's study was based on the prediction that TI-related spontaneous activity could be reduced through masking. Periods of narrowband noise were contrasted with baseline rest periods in 12 patients to show that the masking sound increased auditory cortical activity. However, without an appropriate control group, it is not possible to ascertain whether or not the resting or the sound-evoked activity differed from normal. In contrast, the fMRI study by Melcher and colleagues did include

matched controls. Periods of bilateral broadband noise masker were contrasted with baseline rest periods in seven patients (four with lateralised and three with bilateral TI) and six controls. Melcher predicted that habitual TI would modify the evoked response to external sounds. Specifically, she argued that people with TI would exhibit a different pattern of activity in response to a masker sound compared to non-TI controls. In controls, the sound-evoked activity occurred equally in both left and right inferior colliculi. In patients with lateralised TI however, the noise generated a smaller response on the side contralateral to the TI percept. This result could be explained by two different neurophysiological models (Figure 3). The 'saturation' model proposes that the increased spontaneous activity on the contralateral side limits the magnitude of the evoked response to an external noise (due to saturation of the BOLD response). Within this model it is also plausible that hyperacusis leading to an abnormally large response to external sounds may also partly explain the limits on overall activity in patients with TI. Alternatively the 'physiological masking' model proposes that the presence of the noise masker reduces habitual TI-related activity because it suppresses TI. Although the noise generates a response of normal magnitude, when the two conditions are subtracted from one another the overall response is reduced. However, one finding that appears inconsistent with either model was that the magnitude of the noise-evoked activity in patients with bilateral TI was similar to the controls.

**** Figure 3 here****

A recent fMRI study has similarly examined the pattern of sound-evoked activity in 35 patients with lateralised TI and explained the results within the framework of the 'saturation' model (Smits et al., 2007). Notably, the response to the bilateral music was smaller on the side contralateral than ipsilateral to TI. Evidence for this asymmetry was observed in inferior

colliculus, medial geniculate body and primary auditory cortex, but not in nonprimary auditory cortex. It is interesting to note that, unlike Melcher et al. (2000), this study did find a difference between a further seven patients with bilateral TI and ten controls. While controls showed a left-hemispheric dominance in auditory cortex for the music stimulus, the patients with bilateral TI did not. The reason for this discrepancy between results is unclear. However, it is possible that the degree of individual hearing loss influenced the differences attributed to TI. While Smits and colleagues tested all TI patients irrespective of their degree of hearing loss, the cohort tested by Melcher and colleagues included only a few patients with mild losses and these were at least symmetrical.

The neural effects of TI suppression achieved after residual inhibition has also been examined with PET (Osaki et al., 2005). Residual inhibition refers either to a partial or a complete temporary suppression of TI that lasts approximately 60 seconds after the cessation of a suprathreshold masking sound presented for a period of 30 to 60 seconds (Henry and Meikle, 2000). In contrast to the above studies that reported a change in central auditory activation when the TI sensation was masked by an external sound, Osaki and colleagues found no such changes in auditory cortex when comparing periods of residual inhibition to habitual TI. Surprisingly, they did report a relative *increase* in activity in the anterior temporal pole during residual inhibition. However, we note that this study was conducted with three cochlear implantees who had been deaf for 3-7 years preoperatively and so it is possible that auditory cortical reorganisation after prolonged deafness means that the results are not readily generalisable to patients with more common forms of TI.

Suppression of TI using lidocaine Lidocaine is a local anaesthetic which is used by cardiologists in the treatment of arrhythmia. TI is one of the known short-term adverse effects that can follow an intravenous injection. However, in patients who already suffer from TI, lidocaine can actually suppress the phantom auditory sensation. The percentage of TI patients who experience a benefit from lidocaine is approximately 60% (Simpson and Davies, 1999). Neuroimaging has been used to localise and quantify changes in brain activity following lidocaine administration. In these studies, lidocaine is used to observe modulation of TI-related activity at rest or when listening to a sound. The prediction is that localising the neural effects of lidocaine will reveal the cortical sites mediating TI wherever lidocaine-based TI suppression is associated with reduction in brain activity. The first published pharmacological neuroimaging study used SPECT to quantify local TI-related brain metabolism (Staffen et al., 1999). A single patient with bilateral TI was scanned once with and once without lidocaine injection and the results were compared to a control subject. During habitual TI, resting metabolic activity in the primary auditory cortices was about 13% greater than in the rest of cortex (i.e. 95 and 85 ml/100g/min). Within primary auditory cortex, lidocaine reduced the resting metabolic activity by about 17% (down to 79 ml/100g/min). However, the global effect of lidocaine also reduced activity by 19% (down to 68 ml/100g/min). In the control subject, a rather puzzling finding was that lidocaine exerted *no* global changes in activity. Andersson et al. (2000) also reported a single case study of a patient with chronic bilateral TI using PET. Once again when the patient's TI was suppressed by lidocaine auditory cortical activity reduced, but only in the left hemisphere. Reductions were also observed in right prefrontal and left parietal cortex. Two group studies are worth mentioning here. In the same PET study of noise masking that was previously described, Mirz et al. (1999) also contrasted periods of lidocaine-based TI

suppression with baseline rest periods. For the ten patients who responded to the drug, it was found to reduce activity in right prefrontal and parietal regions regardless of TI laterality, but it did not significantly modulate activity in auditory cortex. The design of a later PET experiment was more rigorous because it included a non-TI control group and also a condition in which a placebo injection was given (Reyes et al., 2002). Not all of the nine patients responded to lidocaine in the same way. In four patients it suppressed TI, in another four it exacerbated TI and in one it had no effect. In right auditory cortex, activity decreased after lidocaine to a greater degree in the patients for whom TI was suppressed, than in those for whom it was enhanced. A non-specific increase in activity due to lidocaine was found in cingulate cortex and a number of subcortical regions including thalamus, and a decrease in activity in the central sulcus. The null effect reported by Staffen et al. (1999) may therefore be a consequence of pooling together activations and deactivations in the analysis. More recently, Plewnia et al. (2007) examined nine patients for whom lidocaine resulted in a transient reduction of TI. Scans obtained during the resting state after lidocaine injection (TI suppression) were contrasted with baseline scans (habitual TI). Statistical group analysis revealed reliable effects of lidocaine within right temporoparietal junction and left middle and inferior temporal cortex. Thus, although the precise cortical locations of the sites of lidocaine action appear to vary across different reports, these results tend to confirm a pivotal role for regions beyond auditory cortex in the perception of TI, including regions engaged in multisensory integration and cognitive function.

The effect of lidocaine on the evoked response to an external sound has not yet been measured in cortex. Nevertheless, there is one case study measuring activity in the inferior colliculus (Melcher et al., 1999). This patient reported lateralised TI which might be predicted to produce an abnormal asymmetrical response to the broadband noise (c.f. Melcher at al, 2000).

Results indicated that as TI was suppressed, the abnormal asymmetrical response to the broadband noise became symmetrical. As the TI percept gradually returned, so did the abnormal pattern of activity. This result is consistent with the saturation model of TI in that lidocaine could decrease spontaneous activity on the side contralateral to the TI percept thus temporarily 'normalising' the response to sound.

It is possible that lidocaine modulates TI by temporarily reducing neural firing and blocking neurotransmission via sodium channels (Chevier et al., 2004). Focal injections in primate sensory cortex have been shown not only to reduce the magnitude of the stimulus-evoked BOLD response, but also to reduce the corresponding multi-unit activity and LFPs (Rauch et al., 2008). A temporary uncoupling of LFP and spiking activity during recovery from lidocaine inhibition suggests that lidocaine affects local sub-threshold synaptic activity as well as spiking output. Lidocaine has a dose-dependent effect on the vascular system causing vasoconstriction at low doses and vasodilation at high doses (Johns et al., 1985). The latter could produce a positive baseline shift in BOLD signal due to an increased concentration of oxyhaemoglobin in the dilated blood vessels. Consequently, it would be unexpected to find a non-specific global effect of lidocaine for a TI patient and not for a control participant when both receive the same dose (c.f. Staffen, 1999). A putative site of action in the central auditory system is consistent with electrophysiological studies in animals that demonstrate reductions in spontaneous activity in A1 and the anterior auditory field (AAF), but is inconsistent with an increase in activity measured in secondary auditory cortex (A2) (Eggermont and Kenmochi, 1998).

Suppression of TI using direct neural stimulation According to the theory of increased spontaneous activity in the central auditory system, treatments to reduce this hyperactivity should immediately suppress TI. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that uses the principles of electromagnetism to alter neural activity by delivering to a focal brain region a series of magnetic pulses of short duration (> 300 μs) at repetition rates of around 1 Hz. This technique has had moderate success in treating a number of disorders that are assumed to arise from neural hyperactivity, including Parkinson's disease (Fregni et al., 2005) and depression (Klein et al., 1999). Not only does rTMS have the potential to provide temporary relief from TI, but it can also be used as a research tool to confirm the direct involvement of specific cortical sites in the generation of TI (see Londero et al., 2006; and Pridmore et al., 2006 for reviews). The aim in the research setting is to first localise TI-related activity with PET or fMRI and to then apply rTMS to the cortical site that has been identified. When TI co-occurs with a hearing loss, it is not possible to clearly attribute the abnormal activity to TI. However, if the subsequent rTMS applied to the site of maximal TI-related activity is successful in reducing TI, then this outcome increases confidence that this cortical site plays a causal role in TI. Two examples of this approach are given. In a PET study, Plewnia et al. (2007) identified, in eight TI patients, individual foci around the temporoparietal junction on the left or right side where activity significantly reduced during lidocaine-induced TI suppression. The temporoparietal junction corresponds to the superior portion of the Sylvian fissure close to auditory cortex. When rTMS was subsequently targeted to this site, six patients reported TI relief. In an earlier case study, de Ridder et al. (2004) reported a relative reduction in the right auditory cortical response to music presented binaurally. While this result is consistent with the left-sided laterality of the hearing loss, de Ridder and colleagues claim that the result also

supports the conclusion that TI-related activity was greater on the side contralateral to (left-sided) TI. In this patient, rTMS was therefore applied to the right auditory cortex and a suppression of TI was reported. An extra-dural electrode was subsequently implanted in the patient's right auditory cortex which after some period of readjustment provided long-term relief from TI. Although requiring replication, these two rTMS studies point to the essential role of auditory cortex and regions of multisensory integration in the perception of TI.

Voluntary modulation of TI by somatomotor movements In humans, the perceptual characteristics of TI are well known to be modulated by various somatic movements such as jaw clenching, lateral eye gaze or finger-thumb opposition. It is proposed that this subtype of TI may follow a failure of cross-modal inhibition within brainstem structures (namely the dorsal cochlear nucleus) that code sensory information from different modalities (Levine 1999a; Cacace, 2003). In a systematic study of 70 patients, Levine (1999b) found that regardless of TI aetiology or hearing status, 68% of patients could modulate the loudness, pitch or location of their TI. We do not provide a comprehensive review of studies that examine these cross-modal mechanisms because activity within the putative origin of this type of TI aetiology (namely dorsal cochlear nucleus) is barely detectable using human neuroimaging techniques. Instead we illustrate some of the neural changes that occur in higher centres of the auditory system that receive inputs from the dorsal cochlear nucleus.

Lockwood et al. (1998) studied four patients with high-frequency hearing loss who were able to control the loudness of their troublesome TI by performing an oral facial movement. In two patients, the movement decreased TI loudness and this specifically reduced activity in the left primary and nonprimary auditory cortex, contralateral to the TI percept. In two patients, the

same movement increased TI loudness and this was associated specifically with increased activity in the left medial geniculate body, although it was not systematically related to TI laterality.

Other studies of patients who could voluntarily evoke TI or increase its loudness have also reported TI-related increases in auditory cortical activity to be located ipsilateral to the side of the percept. Two studies are worth mentioning here. Cacace et al. (1999) reported that one patient with left-sided deafness following neurosurgery was able to elicit left-sided TI by performing repetitive finger-thumb opposition tapping movement with the right hand. Using fMRI, activity was found to increase in the contralateral left temporoparietal junction during the movement. Using PET, Lockwood et al. (2001) measured TI-related activity in five patients with a left-sided deafness following neurosurgery and with left-sided TI that was evoked by a sideways eye movement. Again four out of the five patients showed TI-related increases in left anterior nonprimary auditory cortex, as well as in right prefrontal cortex. A group of four patients with the same TI aetiology exhibited a different pattern of results (Giraud et al., 1999). In contrast, the phantom auditory sensations increased activity in nonprimary auditory cortex and this response was greater on the left side, regardless of the side of TI and the deafened ear. Thus, the authors concluded that elevated spontaneous activity may be associated with TI in those specific cases where somatic movements modulate the sensation, but the driving mechanism probably emerges from subcortical reorganisation and the measured cortical activity reflects the consequence of an ascending abnormal neural signal.

Summary Neuroimaging findings from the various experimental manipulations that modify the TI percept have clearly demonstrated that TI is associated with changes in activity within

auditory cortical and subcortical structures and have confirmed that a mechanism for TI should be sought in the brain. The results are certainly not *in*consistent with the interpretation that TI is associated with increased spontaneous activity in the central auditory pathway. However, one important caveat is often neglected. Interpretations are almost always based on the inference that an increase in the haemodynamic response (either regional cerebral blood flow or BOLD signal) represents an increase in mean firing rate. Simultaneous fMRI and electrophysiological recordings suggest that while in some circumstances this is true (Heeger et al., 2000), it is not always the case. Logothetis and colleagues have repeatedly shown that the haemodynamic response correlates more with overall synaptic activity (measured by local field potentials) than with mass action potentials (measured by multi-unit spiking activity) (Logothetis et al., 2001; Logothetis, 2008). Thus synaptic activity, including excitatory and inhibitory postsynaptic potentials as well as integrative processes such as neurotransmitter release, places the greatest demands on metabolic energy. Strictly speaking therefore, the haemodynamic response primarily reflects the consequences of neural input to a brain region and its processing therein, rather than its output in terms of the firing of projection neurons. While it is reasonable to expect input and output activity to correlate most of the time, when input into a particular brain region primarily plays a modulatory role, neuroimaging experiments may measure activation that does not correlate well with single-unit electrophysiological recordings (Logothetis and Wandell, 2004).

ii) Changes in the temporal firing pattern

Elevated spontaneous firing rate is unlikely to be the sole mechanism of TI and the emergence of a temporal pattern upon what is otherwise random spontaneous firing both within and across neurons has been postulated as a complementary neural abnormality underpinning TI. Both

increased bursting discharges and increased synchronous activity have been recorded electrophysiologically in various auditory structures including inferior colliculus and primary auditory cortex, while in humans the temporal patterns of intrinsic activity have so far been examined only at the cortical level.

Guidance from animal electrophysiological studies

Bursting activity within a neuron Given that an external tonal stimulus can be signalled in the auditory system by neural firing that is phase locked to the signal, it is plausible that TI is consequence of a pathological increase in burst firing that occurs spontaneously but is erroneously interpreted as sound (Moller, 1984; Kaltenbach, 2000). Bursting activity is generally identified when two or more action potentials occur in rapid succession (i.e. a few milliseconds apart) at regular intervals (Figure 2B). While the limit of phase locking within the central auditory system is thought to be about 5 kHz (Evans, 1978), the pitch of TI in humans is usually judged to fall within the high-frequency range (Noreña et al., 2002; Roberts et al., 2006; Konig et al., 2006; Savastano, 2008) and often between 7 and 9 kHz (McCabe and Dey, 1965). Therefore the precise relationship between the periodicity of bursting and the perceived TI pitch still requires some further understanding.

Synchronous activity between neurons Synchrony between neurons can be measured by temporal cross-correlation analysis, a method that quantifies the degree of temporal synchrony between two simultaneously recorded neurons over a period of time (Figures 2C and 2D). Correlated activity between two neurons is indicated in the cross-correlogram as a central peak that becomes higher and narrower the stronger the correlation. Phase locking to the periodicity of

an external tonal signal tends to occur across neuronal ensembles, thus increasing between neurons. Using the cross-correlation technique, Eggermont and colleagues have also reported an increase in the degree of auditory synchronisation after application of quinine. In cat A1, quinine was shown to significantly increase the height of the peak of the correlation between the spontaneous activity recorded across separate electrodes (Ochi and Eggermont, 1997) in a dose-dependent manner. In another study by Ochi and Eggermont (1996) a greater number of auditory neuron pairs showed significantly correlated firing after salicylate application in cat A1, however, the strength of the peak of correlation did not alter.

As is the case for spontaneous stochastic firing rate, there is evidence that the changes in synchrony are spatially coincident with changes in the frequency tuning properties of those neurons. Seki and Eggermont (2003) reported that after tone-induced (6 kHz) hearing loss in cats increased synchrony was largely restricted to regions of A1 where reorganisation of the tonotopic map (6-10 kHz) was observed compared to non-reorganised regions. A similar result has been reported in cat A1 after noise trauma (Noreña and Eggermont, 2003). However, the spatial precision of human neuroimaging methods cannot reliably differentiate changes in synchrony across different portions of the tonotopic gradient.

In summary, the results are generally supportive of an association between TI and an increase in neural synchrony, particularly in the region of tonotopic reorganisation. Obviously, increased spontaneous firing rate within this region does increase the opportunity for synchronous activity, but there is reliable evidence that the increased synchrony is unlikely to be just a statistical artifact of spontaneous firing rate (Bauer et al., 2008). A computational model of TI describes the mechanism by which deafferentation can lead to increases in neural synchrony

within the damaged region of the tonotopic map through compensatory decreases in the gain of lateral connections (Dominguez et al., 2006).

The implication of an increase in synchrony between pairs of neurons in the context of human neuroimaging is worth clarifying. While electrophysiological studies of neural synchrony are performed on a microscopic level generally by computing the degree of cross-correlation across spiking activity for pairs of independent neurons, EEG and MEG measure synchrony on a macroscopic level with signals reflecting synchronous activity across a large population of neurons. Thus, human EEG and MEG studies of spontaneous activity typically examine oscillatory activity, i.e. synchronous activity that has a regular (periodic) temporal structure; a rather different class of neural phenomenon. Some electrophysiological evidence does support the notion that TI is associated with altered slow-rate periodic activity. For example, Kenmochi and Eggermont (1997) have shown in cat A1, individual neurons can have a preferred spontaneous firing periodicity (typically 6-8 Hz) that can be identified by applying autocorrelation analysis methods to the LFP. After administration of salicylate or quinine, the rate of these oscillatory responses decreased (on average from 8.7 to 7.6 Hz) and their strength increased. In humans, microelectrode recordings of thalamic activity in patients with TI undergoing preoperative assessment for the treatment of neurogenic pain have also shown abnormal rhythmic bursting at 4 Hz (Jeanmonod et al., 1996). Therefore, increased oscillatory power or changes in periodicity in the theta frequency range (4 to 8 Hz) may be potential neural signatures for TI.

Human neuroimaging studies

EEG and MEG are applied to investigate oscillatory rhythms in humans in a wide variety of contexts. In humans, oscillatory brain activity is well known to arise during various states of normal arousal and cognition (e.g. Pfurtscheller and Lopes da Silva, 1999). Oscillatory activity in different frequency bands has also been shown to distinguish pathological from normal states (Wienbruch et al., 2003; Osipova et al., 2006; Oshino et al., 2007). The notion of altered thalamocortical rhythms has been proposed to explain the neural underpinnings of various abnormalities in oscillatory activity associated with a range of common neurological conditions including tremor experienced in Parkinson's disease, neurogenic pain, excessive thoughts in depression and phantom sounds in TI (Llinás and Paré, 1995; Llinás et al., 1999). The thalamocortical dysrhythmia model (Figure 4) links the symptomatology with abnormal low frequency (< 10 Hz) and gamma band (> 30 Hz) activity in the resting state. Such abnormalities are supported by animal research and are suggested to arise from a cascade of neural events that are initiated by input deafferentation (in the case of TI by hearing loss) (Jeanmonod et al., 1996; Steriade, 2006). Loss of excitatory input results in the membrane potentials of thalamic neurons becoming hyperpolarised. At these more negative voltages, large-scale, stable slow-rate oscillatory coherence can emerge from an upregulation (or influx) of a calcium current and downregulation of a high-threshold potassium current in the thalamic relay neurons (Jahnsen and Llinás, 1984). Such slow-rate oscillations activate the return corticothalamic pathways and entraining brain structures of the 'non-specific' arousal circuit into the same pattern of theta oscillatory activity. At the cortical level, the focal slow-rate oscillations of cortico-cortical inhibitory interneurons reduce lateral inhibition and disinhibit beta (14 to 30 Hz) and gamma oscillations in neighbouring cortical modules. At the interface between normally innervated and deafferented thalamocortical circuits, abnormal gamma activity is proposed to be maximal

(Llinás et al., 2005). Thus the perceptual experience of TI is proposed to be linked to an increase in this gamma-band oscillatory activity which corresponds to the normal brain rhythm when an external sound is presented (Joliot et al., 1994; Crone et al., 2001). Llinas et al. (2005) speculate that TI is not the result of increased spontaneous activity per se. Rather, TI is considered to be a neural "edge effect" that originates in the cochlea at the point of contrasting 'normal' and 'low' levels of activity and is transmitted throughout tonotopic regions of the ascending central auditory system.

Figure 4 here

Resting state oscillatory activity Although the specific electrophysiological evidence to validate the thalamocortical dysrhythmia model is lacking, the theory makes a number of specific predictions that can be tested in humans using EEG or MEG, namely that TI should be associated with an increase in oscillatory activity in low frequencies (<10 Hz) and in the beta and gamma bands, and that altered gamma activity should be maximal at the edge of the hearing loss in primary auditory cortex. To test some of these predictions, Llinás and colleagues measured spontaneous MEG activity in one patient with TI during rest (Llinás et al., 1999). During habitual TI, the average power of theta-band activity (5 to 10 Hz) over the whole head (normalised with respect to alpha-band activity, 10 to 15 Hz) was greater in the TI patient than in seven out of the nine controls. However, no data were reported for gamma-band activity and so this particular aspect of the model prediction was not tested.

**** Figure 5 here ****

TI-related abnormalities in oscillatory activity have been examined within groups of TI patients. Comparing 17 patients with TI associated with hearing loss with 16 controls, Weisz et

al. (2005a) reported an abnormal average increase in MEG oscillatory power in the delta frequency band (1.5 to 4 Hz). It must be noted that although Weisz and colleagues do not specifically acknowledge Llinás' thalamocortical dysrhythmia, their findings are in line with the concept of altered biorhythms (Figure 5). However, their results highlighted a simultaneous reduction in oscillatory power in the alpha band (8 to 13 Hz) which they attribute to a disinhibition of the 'normal' brain rhythms by the same neural mechanism that Llinás et al. (1999) attributes to changes in the beta band (see also Weisz et al., 2007a). Further empirical studies are therefore required to reconcile these discrepancies. We note that the altered oscillatory activity reported here cannot distinguish changes due to TI from those due to hearing loss because controls were reported to have 'normal' hearing. It is interesting to note that no abnormalities were reported in the gamma frequency band because "downsampling of the data did not permit analysis in this frequency band". Gamma band activity was examined in a subsequent study in which data were acquired at the same sampling rate (678 Hz) and filtered using the same bandwidth (1 to 200 Hz), but were not downsampled (Weisz et al., 2007b). 26 TI patients were compared with 21 controls. An abnormally high level of oscillatory power in the high-frequency (40 to 90 Hz) gamma range was reported, particularly in the 50 to 60 Hz range. Further analysis of the gamma-band activity revealed a significant relationship between the laterality of TI and a contralateral increase in activity in the 55-Hz region suggesting that the dominance of oscillatory power in the gamma band (~55 Hz) is a fundamental neural correlate of the TI percept. In patients reporting bilateral TI, abnormal gamma activity was not lateralised. Confirming the previous result, an increase in delta activity (1 to 3 Hz) and decrease in alpha activity (8 to 12 Hz) were also reported. A recent EEG study has localised TI-related gamma activity (40-80 Hz) to the temporal (possibly auditory) cortex (Ashton et al. 2007). However,

Ashton et al. found no consistent relationship between the laterality of TI and the side of maximal gamma activity (ipsilateral in five patients and contralateral in three). This finding contradicts the claim by Weisz et al. (2007b) that the scalp distribution of gamma activity determines TI laterality. Also in contrast to previous MEG studies, Ashton et al. found no evidence of abnormal activity in any of the low-frequency bands. Examining EEG or MEG data as simple power maps does not adequately address hypotheses about the underlying mechanisms of TI. In particular, by failing to localise the cortical sources of the abnormal activity to precise locations, specific predictions arising from the model cannot be tested. For example, the thalamocortical dysrhythmia model would predict that elevated gamma activity originates within primary auditory cortex most notably at the sloping edge of the hearing loss. However, current analysis methods for spatial localisation of EEG and MEG data are too imprecise to test this prediction.

Suppression of TI using noise maskers and residual inhibition Demonstrating altered spontaneous activity during habitual TI does not necessarily prove a causal link between abnormalities in oscillatory activity and the TI percept, especially when hearing loss is present. A better test of this theory would be to show differences in gamma-band oscillatory activity according to whether the TI percept is present or absent in the same group of patients. Noise masking and residual inhibition present two different ways to modify individual TI. To explain the mechanism by which noise masking can suppress TI, Llinás et al. (1999) have suggested that the noise generates excitatory drive and depolarises the underlying thalamocortical circuits, thus reducing the abnormal pattern of theta oscillatory activity. The thalamocortical dysrhythmia theory makes the specific prediction that noise masking to suppress TI should reduce theta and

gamma oscillatory power (Llinás et al., 2005). Preliminary MEG support from a single case study (Llinás et al., 2005) indicates that noise masking reduced power in the theta frequency band (~7 Hz) within the auditory cortex relative to the habitual TI condition (Figure 6). Again, no data were reported for gamma-band activity and so this particular aspect of the model prediction was not tested.

****Figure 6 here****

The effect of residual inhibition on gamma-band oscillations has been investigated using MEG (Kahlbrock and Weisz, 2008). Spontaneous brain activity in ten patients with TI was contrasted between periods of residual inhibition and periods of habitual TI following an ineffective (control) masker. During residual inhibition, a significant reduction of power in the delta frequency band was reported arising from the temporal lobe. However, TI suppression did not alter activity in the alpha or gamma frequency bands, as might have been predicted from the thalamocortical dysrhythmia theory. To explain this null result, the authors suggest that prolonged TI might lead to self sustaining abnormal low- and high-frequency oscillations.

The physiological effects of noise masking and residual inhibition are unlikely to be identical since, unlike masking, residual inhibition suppresses TI for some time after the noise has ceased. Eggermont and Roberts (2004) have suggested that in residual inhibition, the suprathreshold masker inhibits the deafferented region of the tonotopic map by modifying the synchronous neural activity that underlies the TI sensation. According to their model, the loss of thalamic input and feed-forward inhibition on cortical neurons (leading to an increase in neural synchrony) extends throughout the deafferented region of the tonotopic map. For Eggermont and Roberts, TI reflects synchronous activity among deafferented neurons that retain their functional specialisation and the resulting activity is perceived as a tonal sound corresponding to its location

in the tonotopic map. This position differs from that of Llinás who proposed that synchrony is most affected at the edge of the deafferented region. Hence one might presume that, for Llinás, the dominant TI pitch should correspond to the edge frequency not at some place within the zone of hearing loss. Eggermont and Roberts (2004) do not speculate about the oscillatory frequency of this abnormal synchronous activity and so one cannot draw on human EEG and MEG data to distinguish between the two different synchrony models.

Summary Evidence from animal and human studies generally supports neural synchrony as a possible mechanism of TI. Often neuroimaging studies make direct inferences from the animal work to explain the neural mechanisms underlying their EEG or MEG data. As our review has shown, this interpretive leap may not be valid here because synchrony between neurons represents a different class of neural phenomenon from that of oscillatory population activity. Another issue that is rarely discussed in the neuroimaging work concerns whether or not it is reasonable to assume that the periodicity observed microscopically in the pattern of neural spiking activity and the periodicity observed macroscopically in the rhythms of postsynaptic activity indeed represent the same neural process. Macroscopic oscillatory activity can be measured by EEG and MEG only if it occurs in phase across an extremely large neural population and it can also occur in combination with bursting activity. These fundamental assumptions should be scrutinised empirically using multimodal recording approaches.

iii) Reorganisation of the cortical tonotopic map

Guidance from animal electrophysiological studies

Many central auditory structures are tonotopically organised. In other words, neurons selectively respond to characteristic frequencies and there is an orderly progression of frequency tuning in bands across distinct auditory fields. Tonotopic organisation is established in the cochlea and is maintained throughout the central auditory pathway to the primary auditory fields. Deafferentation of a portion of the cochlea reduces input to the corresponding portion of the tonotopic map in each field. A maladaptive response to this loss of input causes expansion of the tonotopic map so that this affected portion now becomes responsive to the adjacent frequency at which hearing threshold is normal - the lesion-edge frequency (Figure 7). Of relevance for human neuroimaging studies, animal research has shown that a restricted cochlear lesion in adult animals drives neuroplastic changes in the frequency gradient within primary auditory cortex (Robertson and Irvine, 1989; Kaas, 1991, Rajan et al., 1993; Schwaber et al. 1993; Irvine et al., 2001). One theory of TI proposes that it is a consequence of such cortical reorganisation (e.g., Salvi et al., 2000a). This neural mechanism of TI specifically links the TI pitch to the lesion-edge frequency (c.f. Hazell and Jastreboff, 1990) since it assumes that the tonotopic expansion directly causes the phantom sound. Rajan and Irvine (1996) suggest that in order for such expansion to occur, hearing loss must be steeply sloping at ~50 dB per octave since they failed to demonstrate injury-induced reorganisation in cats with gradually sloping losses.

**** Figure 7 here ****

Human neuroimaging studies

An early study using PET reported more extensive auditory cortical activation in response to a 2-kHz tone in a group of four TI patients with mild-to-moderate hearing loss (>2 kHz from 30 to 70 dB) compared to controls with hearing levels of 25 dB or better from 0.25 to

8 kHz (Lockwood et al., 1998). While 2 kHz corresponded to the edge of the hearing loss, the TI pitch was matched near the peak of hearing loss, not the lesion edge. Therefore, this result is not fully explained by the tonotopic reorganisation model of TI. Moreover, the sensitivity of PET as a measure of tonotopic reorganisation is somewhat questionable. For example, in their review of PET for functional mapping within primary auditory cortical fields, Johnsrude and colleagues (2002) conclude that the spatial resolution of PET is not sufficient to address questions of a sufficiently fine anatomical grain.

Alternatively, the amplitude of the evoked N1 (EEG) and N1m (MEG) response can be used as an indicator of cortical expansion because such reorganisation increases the size of the neural population responding to a single-frequency tone at the lesion edge. It also increases the distance between the response to the tone at the lesion edge and a control tone within the region of normal hearing. Using MEG, Dietrich et al. (2001) examined eight patients with high-frequency hearing loss, seven of whom also complained of TI. For each patient, tone bursts were presented at the lesion-edge frequency and two control frequencies within normal hearing. Tone bursts of 0.5, 1, 2, and 4 kHz were used in the control group. In seven of the eight patients, the contralateral N1m response was significantly enhanced for the tone at the audiometric edge compared to control tones supporting the claim for tonotopic expansion at the lesion edge. However, the results provide no support for the putative association between cortical reorganisation and TI. Specifically, no significant correlation was found between the amplitude of the dipole moment for the N1m deflection and the reported scores for TI annoyance and the authors did not specify whether the patient without an enhanced N1m was the same individual who was TI-free.

**** Figure 8 here****

A somewhat different pattern of results was obtained by Weisz et al. (2005b) which contradicts the predictions of the simple model of reorganisation considered hitherto. In their MEG study, Weisz and colleagues examined the amplitude of the N1m response in 14 TI patients with moderate to severe high-frequency hearing loss and 11 normally hearing controls. Similar to the previous study by Dietrich et al. (2001), the response to a lesion-edge frequency was compared to that for a control frequency chosen within the range of normal hearing. In contrast however, in the TI group the N1m response was significantly enhanced for the *control* tone rather than the tone at the audiometric edge. This group result was significant only for the right hemisphere, but converging support for the importance of the right hemisphere was provided by the positive correlation (on the right side and not on the left) between the relative amplitude of the dipole moment for the lesion-edge tone and TI intrusiveness.

Changes in the amplitude and the dipole moment of the N1 response may also alter the location of the source estimate. The cortical reorganisation model would predict a deviant source localisation for the lesion-edge frequency. This hypothesis was tested by Weisz and colleagues (2005b). Their results of dipole fitting indicated an abnormal source location for the lesion-edge, but again only in the right hemisphere and without any systematic association between the degree of deviance and TI-related distress. Hence the authors concluded that although some aspects of the data were consistent with the map reorganisation hypothesis, explanations of the hemispheric differences and the relationship to TI remained unresolved.

An early MEG study by Mühlnickel and colleagues (1998) is often cited in support of the tonotopic reorganisation model of TI. In this study, four single-frequency tones (from 1 to 8

kHz) were presented, one of which corresponded to the dominant TI pitch in individual patients. For the group of ten TI patients, the contralateral N1m response to the TI pitch was reported to shift on average 2.7 mm from the axis of the linear tonotopic gradient defined by the response to the other three tones (Figure 8). Such a shift from linearity was not found in the normally hearing controls. In our opinion, the results and the interpretation are problematic on a number of levels. First, according to Rajan and Irvine (1996), the hearing loss was probably insufficient to drive such dramatic cortical reorganisation since thresholds were at worst 25 dB. Second, the N1/N1m dipole analysis for tonotopic mapping has been strongly criticised for its reliance on untenable assumptions and its lack of spatial precision (Lütkenhoner et al., 2003). Third, the observed shift in dipole location was for a TI pitch corresponding to the region of hearing loss, not for the lesion-edge frequency as predicted by the reorganisation hypothesis as proposed by Hazell and Jastreboff (1990).

The steady-state response (SSR) has been proposed as a more spatially specific marker for frequency-specific activity than the evoked N1/N1m transient because it is believed to arise within primary auditory cortex (Ross et al. 2002). The SSR is a component of the event-related potential that reflects a sustained response that is phase-locked to a periodic stimulus, with the best response occurring to sounds presented at a rate of 40 Hz. Diesch et al. (2004) investigated the 40-Hz SSR as an MEG marker for TI and examined whether an abnormal auditory evoked response was more closely associated with the lesion-edge frequency or the TI pitch. In this study, six carrier frequencies were presented including one at the audiometric edge, one corresponding to the TI pitch, two below and two above the sloping edge of the hearing loss. Ten patients were tested; all with TI but various degrees of hearing loss. The SSR amplitude (dipole power) was significantly enhanced for carrier frequencies matched to the TI pitch above the

audiometric edge. The mechanism relating TI to tonotopic reorganisation was supported by the significant positive correlation between normalised SSR amplitude and TI intensity and intrusiveness, even after the influence of hearing loss had been partialled out from the multiple regression. In a similar MEG study, Wienbruch et al. (2006) measured the 40-Hz SSR for eight carrier frequencies (384 to 6561 Hz) in a group of 28 TI patients (14 bilateral, 11 left-sided, 3 right-sided) and 17 normally hearing controls. Audiometric evaluation was not performed, but hearing thresholds measured in the MEG scanner were elevated for the TI group compared with the control group across all frequencies, especially at higher frequencies. Dipole modelling of the SSR data for the TI group revealed an abnormal frequency organisation with a flattening of the gradient above 1 kHz in both hemispheres. This weak expression of tonotopy is consistent with the animal model of altered frequency representation after hearing loss. Nevertheless, the data failed to support any systematic relationship between SSR variables (deviation from the linear frequency gradient and dipole power) and properties of the TI sensation (loudness, pitch and duration). To explain these results, the authors speculated that nonprimary auditory regions beyond the core tonotopic fields might determine the perception of TI.

A different approach considers the auditory mismatch negativity (MMN) which is a differential rather than an absolute evoked response. The MMN provides a discrimination index for a deviant tone in a sequence of repeating standards. It is a negative potential with a post-stimulus latency of 100-250 ms and a source that includes auditory cortex. Weisz et al. (2004) hypothesised that if the lesion-edge frequency is over-represented in the tonotopic map then it should elicit a larger MMN than would a single-frequency tone in the region of normal hearing. Fifteen TI patients were compared with audiometrically matched controls. Abnormal MMN responses were specific to the lesion-edge frequency in the TI group. However, in contradiction

with the reorganisation model, source localisation of the N1 implicated the involvement of anterior brain regions in the abnormal MMN, more suggestive of a role for emotional and cognitive centres in TI than for the central auditory system. Convergent evidence for this interpretation was provided by a significant correlation between the degree of the anterior shift and the degree of self-reported psychological distress as measured by a TI questionnaire.

Summary Evidence from EEG and MEG in humans is generally consistent with an expansion of frequency-specific auditory cortical responses corresponding to the audiometric edge in patients with sloping high-frequency hearing loss. More direct evidence to link neurophysiological markers of reorganisation with perceptual variables related to TI is however somewhat mixed and therefore there is no conclusive evidence that this type of neural plasticity underpins TI.

Neuro-modulatory influences

It is well established that co-morbid symptoms of TI include stress, anxiety, and depression; factors that affect psychological and emotional well-being (Hiller et al., 1997; Andersson and McKenna, 1998; Andersson et al., 2006). Some people can tolerate their TI and accept it as part of their everyday environment. Others find their TI intolerable and as a consequence it can lead to other clinical symptoms such as poor concentration, sleep disturbance, fear, anxiety and depression (Tyler and Baker, 1983). The limbic system is involved in affective processing through its influence on the endocrine and the autonomic nervous systems, as well as its connections to the prefrontal cortex. The system includes hippocampus, amygdala, hypothalamus and cingulate gyrus. The involvement of limbic and autonomic nervous systems that subserve human emotions is postulated to play a role in TI (Jastreboff, 1990) and the negative emotions

associated with TI may be mediated by direct connections between the auditory cortex and limbic system.

A number of animal studies have reported the involvement of the limbic system in TI. To the best of our knowledge, there are no published electrophysiological data on this issue but there are a number of reports on c-fos expression which can provide an indirect marker of activity because it is a transcription factor that is expressed during neural firing. Salicylate and exposure to impulse noise increased c-fos expression in the amygdala, thalamus, frontal and cingulate cortices, as well as in hypothalamic and brainstem regions (e.g. locus coeruleus) involved in behavioural and physiological defensive reactions in gerbils (Wallhäuser-Franke, 1997; Wallhäuser-Franke al., 2003; Mahlke and Wallhäuser-Franke, 2004). Activation of these areas was associated with stress, aversive-affective components as well as autonomous reactions associated with treatment and TI. In another study in hamsters the increase of c-fos expression was observed in structures such as locus coeruleus, lateral parabrachial nucleus, and certain subregions of hypothalamus and amygdala (Zhang et al., 2003).

In humans, a number of neuroimaging studies have also identified TI-related activity in limbic regions (see Figure 9). Traditional MEG methods of analysis remain rather insensitive to signals arising from deep sources within the brain since the magnetic fields decay rapidly over distance. Nevertheless, using alternative analysis techniques, several recent MEG studies have reported fear-related responses in the amygdala (Moses et al., 2007; Cornwell et al., 2008). Studies of TI have typically used PET and MRI for spatial localisation of limbic involvement. An early neuroimaging study used SPECT to identify altered patterns of resting-state cerebral blood flow in two patients with TI (Shulman et al., 1995). Compared to five controls, both patients showed decreased metabolic activity in bilateral hippocampus and amygdala and

prefrontal cortex. Regions of altered activity were also reported in other brain regions, but these were inconsistent across patients. The authors suggest that the abnormal activity may reflect a dysfunctional neural network originating in auditory cortex and extends to other areas, including the limbic system. A positive correlation has also been reported between the level of anxiety and resting-state brain activity in left and right anterior cingulate cortex and the caudate nucleus (Gardner et al., 2002). Although not traditionally considered part of the limbic system, the caudate nucleus is a subcortical structure that may play a role in regulating the transmission of affective information between the thalamus and the prefrontal cortex. Supporting evidence has been shown in a study that presented people without TI with aversive, high-pitched tonal sounds, assumed to mimic TI (Mirz et al. 2000a). This PET study revealed sound-related activity in the amygdala/parahippocampal gyrus and hippocampus, bilaterally.

**** Figure 9 here ****

Several other studies have reported the extra-auditory effects of manipulating the TI percept. Using PET, Mirz et al. (2000b) reported that both noise masking and administration of lidocaine reduced activity in left amygdala and right prefrontal cortex. For the masking group, activity also reduced in the right anterior cingulate gyrus. Abnormal left hippocampal activation has been reported in three patients with right-sided TI both in response to a change in the loudness of the TI and in response to external sound stimulation (Lockwood et al., 1998). Several studies have reported the involvement of additional centres in prefrontal cortex that possibly subserve selective attention. For example, Mirz et al. (1999) found that reducing TI by using either noise masking or lidocaine reduced activity in right middle frontal gyrus for all patients regardless of the laterality of TI. However, no changes were found in the limbic system. As in TI

patients, Mirz et al. (2000a) also found that in normal listeners, aversive sounds engaged the middle frontal gyrus, more so on the right side.

Anatomical changes in the gray- and white-matter tissue have also been identified in limbic structures using voxel-based morphometry to statistically contrast anatomical scans from a group of TI patients and matched controls (Mühlau et al., 2006). In this group, TI was associated with a decrease in gray-matter volume in a subcallosal region that the authors interpreted as including nucleus accumbens, but also appears to extend across part of the anterior cingulate gyrus. The nucleus accumbens has connections with the thalamus and prefrontal cortex and Muhlau speculated that it may play a role in the long-term habituation to TI. No effects were reported for auditory cortex. More recent evidence challenges this null result. Schneider et al. (2009) re-evaluated the effect of hearing loss and TI on the gray-matter volume of the postero-medial part of Heschl's gyrus using a more anatomically precise measurement procedure. Results revealed a reduction in the volume of Heschl's gyrus in patients with TI compared to controls and further analysis demonstrated that this difference was unrelated to hearing loss. Schneider and colleagues (2009) suggest that voxel-based morphometry is rather insensitive for revealing volumetric changes, particularly for highly convoluted cortical surfaces exhibiting a high degree of individual variability, such as the auditory cortex.

Brain regions do not operate in isolation but are functionally connected to one another such that the output of one region can drive the activity recorded in another. In order to understand the complexity of the neuro-modulatory influences in TI, neuroscientists must start to examine these dynamic networks of activity. Intrinsic connectivity can be measured from the

resting-state signal, while connectivity underlying specific perceptual or cognitive processes is typically measured while performing experimental tasks. The millisecond sampling rate of EEG and MEG can be used to investigate synchrony and examine large-scale integration of brain regions. A recent MEG study has investigated functional connectivity within a putative TI network by evaluating synchronised activity in the frequency domain between signals recorded at eight different brain sites (Schlee et al., 2008). These eight regions were located in the left and right frontal, temporal, and parietal lobes and in anterior and posterior cingulate cortex. Schlee and colleagues hypothesised that while sounds typically engage this network, a tone corresponding to the TI pitch (i.e. a tone at the audiometric edge) would evoke greater synchrony within the network than a control tone more than one octave below the audiometric edge. Twelve patients with hearing loss and TI and ten normally hearing controls were recruited. Not only was there a significant interregional interaction for the TI pitch in the TI group compared to controls, but there was a correlation between the strength of phase synchronisation and the subjective ratings of TI intrusiveness, for the links between anterior cingulate and right parietal lobe and right frontal lobe, respectively. While the results from this study are particularly intriguing because it attempts to statistically assess the operation of the neuromodulatory influences, the conclusions are somewhat limited in their precision of spatial localisation, their ability to assess the role of hearing impairment, and their lack of individualised stimuli properly matched to the TI pitch. Further studies of functional connectivity are required to validate these preliminary. fMRI methods can also be used to explore such networks and low-frequency connectivity in BOLD signal appears to correlate well with EEG coherence (Laufs et al., 2003). Connectivity analysis has the potential to provide the functional linkage between TI and the associated

perceptual, psychological and emotional factors. However, to date we could find only one unpublished report of this approach (Langers and Melcher, 2008, conference report).

Conclusions

The results of non-invasive human neuroimaging studies have validated the claim that TI is associated with changes in structure and function at various sites in the central auditory system. One of the significant contributions of human neuroimaging concerns its ability to define brain centres involved in the psychological aspects of the disorder, such as the limbic system. Further work to determine correlations between the amplitude of the response in these structures and the reported scores for TI annoyance will be important for corroborating a neurophysiological model of the TI network. Nevertheless, it remains a challenge to synthesise the current body of data into a set of firm conclusions regarding the key mechanisms underpinning TI within the auditory system.

This overview has highlighted two key themes that recur throughout each of the three sections (i-iii) describing how neuroimaging has been used to examine the potential neural mechanisms of TI. The first is a common disregard for the conceptual challenges faced when predicting and interpreting human neuroimaging results based on models of TI predominantly derived from animal research. The second concerns the somewhat inconsistent results across neuroimaging studies, even those reported from the same laboratory. Our discussion expands on each of these two themes in turn.

Regarding the first of these issues, the main problem is that the translation from microscopic neural events recorded in animals with TI to macroscopic patterns of brain activity recorded in humans with TI is not straightforward. The assumptions being made when drawing

conclusions from the human neuroimaging data are not always clearly articulated and so the functional significance of these results might risk being over-interpreted by the non-specialist reader. For example, the coupling between local neural activity and the BOLD response is still unclear. In fact, the fMRI community is still actively engaged in debate over this issue. While it is not necessarily in the domain of TI specialists to direct research to this basic neuroscience question, our first recommendation for future progress in TI would be to encourage collaborative neuroscience to integrate animal and human work on TI in order to obtain sufficient empirical data to define the relationship between invasive and non-invasive recordings of the same neural phenomenon. However, this goal may be difficult to achieve because it requires considerable cooperation between specialist teams, often geographically separated. An alternative approach could be the use of multiple, complementary recording methods in the same animal or human to provide convergent evidence. Such a multimodal approach would not only overcome the shortcomings of individual techniques, but would also increase confidence in the scientific interpretation of the data with respect to a particular neurophysiological model of TI. For example, a particular prediction could be tested in the same animal using neural data recorded at both microscopic (e.g. spiking activity) and macroscopic (e.g., LFPs and BOLD signal) scales (c.f. Logothetis et al., 2001). For humans, it is well known that the spatial and temporal limitations in EEG/MEG and fMRI can be overcome by acquisition of both types of non-invasive data in the same participant using the same experimental paradigm (Salek-Haddadi et al., 2003; Hamandi et al., 2004). Similarly then, perhaps a more reliable classification of the underlying neural abnormality in an individual TI patient could be obtained by integrating fMRI with EEG/MEG data so that the differential sensitivity to potential spatial and temporal signatures of TI, respectively, could be exploited. Unfortunately, access to facilities, scanning

costs and limited expertise in the different human neuroimaging methods might limit the practicality of multimodal recording.

Regarding the second issue of inconsistent results across neuroimaging studies, we note that different research groups sometimes reported contradictory results (e.g. Hoke et al., 1989; Jacobson et al., 1991; Attias et al., 1993), and occasionally even the same group fails to replicate their own earlier findings (e.g. Weisz et al., 2007a; Kahlbrock and Weisz, 2008). Perhaps one reason for this is that TI is a complex disorder with a diverse aetiology and symptoms. Poor replicability could simply be indicative of the variability between TI patients. Hearing status is one of the key characteristics commonly associated with TI and would obviously influence patterns of auditory activity, yet most studies do not report this information while the ones that do average auditory responses from patients with varying degrees of hearing loss (Attias et al., 1993), rather than factor out the contribution of hearing loss (c.f. Diesch et al., 2004). An additional comorbid symptom that might also exert a significant influence on patterns of auditory activity includes hypersensitivity to external sounds (hyperacusis). The importance of controlling for hyperacusis has been highlighted in a recent conference report demonstrating that the increase in neuronal excitability to sounds in TI patients may be ascribed to hyperacusis rather than to a mechanism specifically related to TI (Gu et al., 2008). It is therefore recommended that the characteristics of patients forming a 'TI group' are as closely matched as possible, in terms of aetiology, duration, severity and laterality of TI, age, audiometric profile and other relevant comorbid factors such as depression, anxiety as well as hyperacusis. A related consideration affecting consistency of research outcomes is that of comparing TI patients to an appropriate control group. In many of the studies reviewed here, TI patients with varying degrees of hearing

impairment were compared to a control group of normally hearing participants (e.g. Weisz et al., 2005a; Wienbruch et al., 2006; Weisz et al., 2007a). Clearly, these results cannot separate out those altered patterns of neural activity due to hearing loss from those specifically attributable to TI. Looking back at some of the early days of human functional neuroimaging in TI, Lockwood et al. (1998) clearly emphasised the need for proper control groups to decide whether plastic changes were the result of TI, cochlear damage, or a combination of the two and yet, more than a decade on, most studies still employ controls that are not audiometrically matched to their TI patients

Given such diversity across participants, we might even consider the merits of moving away from group comparisons all together and instead report individual cases. A case study approach would provide a detailed systematic assessment of the perceptual characteristics of TI (especially its spectrum and its loudness) and psychological attributes of the individual (c.f. Jastreboff, 1990) and attempt to relate these to the recorded patterns of neural abnormality. In the field of cognitive neuropsychology, the case study approach has certainly proved to be a powerful scientific tool for testing hypotheses relating to a specific cognitive model. Due to the heterogeneity of TI patients, this approach is potentially more informative than when data from a group of poorly matched TI patients are averaged together. In combination with the multimodal neuroimaging approach discussed earlier, the case study could be a powerful tool for providing strong empirical support for or (perhaps more importantly) refutation of a particular hypothesis about TI.

Another factor with the potential to determine inconsistency concerns the power of the statistical test to accept the null hypothesis when it should have been rejected (Type II error). Increasing sample size is the most common way to increase statistical power, although sensitivity

can also be improved by increasing the reliability of the individual measure or by using well-matched controls. With respect to sample size, many neuroimaging studies draw conclusions about the underlying TI pathophysiology using group statistics with fewer than ten patients (e.g. Giraud et al., 1999; Kadner et al., 2002; Lockwood et al., 1998; 2001; Osaki et al., 2005). While such analyses might be adequate for characterising the common pathophysiology in that particular sample of patients, little can be inferred about the mechanisms underlying TI in the wider population. In statistical terms, this distinction is one of 'fixed' versus 'random' effects. Fixed and random components describe the variability in the brain signal. The fixed effect component represents the common effect among patients, whereas the random effect shows the variation of activation between different patients. Only random effects can lead to general conclusions but, to achieve this, a large number of patients (> 20, Thirion et al. (2007)) are needed to provide high confidence in the parameter estimates of the statistical model. Small numbers of patients lead to low degrees of freedom in variance estimation and yet such small groups are common in human neuroimaging studies of TI.

The final factor concerns the different approaches to data analysis across research sites, especially for EEG and MEG data. Whereas a common approach in fMRI is to localise stimulus-related BOLD responses using the general linear model, MEG and EEG researchers are faced with a range of different choices about the form of the input data and the analysis method. The input data can be either transient, stimulus-evoked responses within a selected time window or more sustained, stimulus-induced responses. The source of this response can then be estimated using dipole fitting or distributed source modelling. The latter includes minimum norm (Hammalainen and Ilmoniemi, 1994), LORETA (Pascal Marqui et al., 1994), MUSIC (Mosher et al., 1992), DICS (Gross et al., 2001) and beamformers (Robinson and Vrba, 1999; Sekihara et

al., 1999); each of which makes a different set of fundamental underlying assumptions. Thus, in making choices to solve the inverse problem, variability is introduced to the outcome of the analysis.

With these recommendations in mind, we hope that the full potential of non-invasive neuroimaging techniques will soon be realised to add real scientific value in the search for models of TI pathophysiology. The goal to better inform the development of new treatments is one that should motivate this worthwhile endeavour.

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Figure legends

Figure 1 The mean association between the profile of hearing loss and TI spectrum (estimated from individual data reported by Konig et al., 2006). The mean function represents the data from 24 patients who matched the dominant pitch of their TI to a single frequency tone. TI pitch is represented by the vertical bars. The arrow points to the mean audiogram edge of the hearing loss. Note that most patients matched their sensation to the region of hearing loss.

Figure 2 Schematic representations of four different patterns of spontaneous neural activity for an ensemble of six cortical neurons (lower traces) and the associated hypothetical MEG/EEG signal (upper traces): A) stochastic spiking activity generates no related MEG or EEG activity; B) stochastic bursting activity also elicits no related signal that can be detected macroscopically; C) synchronous spiking activity also generates an aperiodic MEG/EEG signal; D) synchronous bursting activity also generates an aperiodic MEG/EEG signal possibly of higher amplitude than in C.

Figure 3 A) Abnormal asymmetry of subcortical activation in response to a bilaterally presented noise masker in a patient with right-sided TI (left panel) and a healthy control (right panel). Arrows point to the inferior colliculi. B) The saturation and physiological masking models describe possible physiological causes for the relative abnormally weak activation in the side contralateral to the TI. Comparisons are made to a control model in the absence of TI. For each model, the grey bars represent the relative magnitudes of activity associated with habitual TI 'sound off' and 'sound on' conditions. Dark grey represents residual TI-related activity and light

grey represents sound-related activity. In the saturation model, the dashed lines represent the minimum limit for BOLD (fMRI) activity. The black bars show the resulting differential activation determined by subtracting the total neural activity in the 'sound off' condition from the 'sound on' condition (Melcher et al., (2000), modified with permission from The American Physiological Society).

Figure 4 A thalamocortical circuit proposed to underpin symptoms associated with a number of neurological disorders, including TI. Two interlinked thalamocortical circuits generate low (left) and high (right) frequency spontaneous oscillatory activity. Within each circuit, a specific thalamocortical pathway comprises relay neurons (black dotted line) that project from the thalamus and synapse onto cortical pyramidal neurons (black solid line) and cortical inhibitory interneurons (upper grey dashed line). A non-specific thalamocortical pathway comprises relay neurons (grey solid line) that project from thalamus and synapse onto cortical neurons in the superficial layers. Both pathways provide direct thalamic feedback in a collateral projection to the reticular thalamus (lower grey dashed lines). Indirect thalamic feedback occurs in a return pathway from pyramidal cortical neurons that synapse onto the thalamic input neurons and onto the reticular thalamic neurons. Abnormal spontaneous firing is proposed to entrain intrinsic biorhythmic activity that generates TI. Redrawn from Llinas et al., 1999 (with permission).

Figure 5 MEG Power spectrum averaged over all sensors (n=148) showing abnormal resting state activity in TI patients compared to healthy controls. Note the significant increase in low frequency power around 2 Hz (delta band) and the decrease in power at 10 Hz (alpha band). From Weisz et al. (2005).

Figure 6 MEG power spectrum representing activity from all sensors (n=148) from a single TI patient showing the effect of masking on resting state brain activity. Note the reduction in low frequency power at 8Hz (alpha band) when the masking sound was applied. Redrawn from Llinas et al., 2005 with permission.

Figure 7 Two schematic representations showing the relationship between hearing profile and tonotopic representation of frequency in the central auditory system for normal hearing thresholds (A), and steeply sloping high frequency hearing loss (B). In A, a normal audiometric profile is represented cortically in bands of neurons with iso-frequency tuning curves. This is schematically portrayed here with tuning shifting progressively in octave bandwidths. In B, high frequency hearing loss distorts this linear progression with an over-representation of the lesion-edge frequency.

Figure 8 Shift in the cortical representation of the frequency corresponding to the dominant TI pitch, as assessed by MEG source localisation (Muhlnickel et al., 1998; Copyright (1998) Proceedings of the National Academy of Sciences, U.S.A reproduced with kind permission). The upper panel shows the result of dipole fitting for the contralateral response to four single-frequency tones in a patient with left lateralised TI with a pitch of 6000 Hz. The lower panel shows the result for one healthy control. The triangle represents the location of the response to the tone that was matched to the TI pitch. The circles and the line represent the standard tone location and trajectory of the dipole locations respectively.

Figure 9 The key limbic system structures postulated to be involved in TI perception: anterior cingulate (ACC), hippocampus (Hi), and amygdala (Am). Additionally prefrontal cortex (PFC) and auditory cortex (AC) are labelled since these are often also implicated in the neural basis of TI.

MRC Institute of Hearing Research

Dear Prof Eggermont,

My two co-authors and I would like to thank the second reviewer for further comments and also for your decision to reconsider the manuscript. We have now made further substantial changes while keeping in mind the main concern of the reviewer. Below, we provide a comprehensive set of responses explaining how we have dealt with each comment.

Reviewer #2: Adjamian et al., "The mechanisms of tinnitus: Perspectives from human functional neuroimaging"

General Comments

The organization of the revised manuscript has been streamlined and condensed to a fair degree and the manuscript reads better than before. However, the manuscript still needs a good deal of work in order to serve as a coherent and synthetic review of the imaging literature dealing with tinnitus. The review should focus more tightly on what functional imaging can tell us about the sources of tinnitus in the brain and potential mechanism. There is still far too much emphasis on reviewing the electrophysiological studies and less space devoted to a detailed analysis of prior human imaging studies.

We appreciate this stance by the reviewer regarding the inclusion of animal studies in a review of human neuroimaging literature. However, when discussing the mechanisms of tinnitus, some references to previous animal studies are unavoidable because most of our current knowledge regarding the pathophysiology of tinnitus has come from studies in animals and also because most authors of neuroimaging studies interpret their findings in the light of these same animal studies.

To address the reviewer's concern in our revised manuscript, we have taken a number of steps.

Firstly, in each of the three main sections reporting on the three potential mechanisms we have renamed the first subheading 'Guidance from animal electrophysiological studies'. Our aim here is **not** to provide a comprehensive review of the animal work itself, but to provide only a relevant background to the interpretation of the human neuroimaging work. Consequently these sections have been radically rewritten, as well as shortened in length. We highlight the relevance and significance of the findings for human neuroimaging studies.

These changes are too lengthy to explain in full in this cover letter, but we provide an example of the emphasis on the relevance of the animal work to human studies. With respect to increased spontaneous stochastic firing rate on page 10, we include the following paragraph: "The implications of this result for human neuroimaging are worth clarifying. If an abnormal spontaneous stochastic firing rate occurs in only a small part of the tonotopic map, then the change in the population response may be too little to perturb the neuroimaging signal. In fMRI for example, one voxel would typically therefore encompass the entire nucleus of the inferior colliculus because it has a volume of about 0.032 cm^3 (equivalent to the volume of a cube with a 3 mm side). Although frequency specificity within primary auditory fields can in principle be distinguished using fMRI, statistical sensitivity to fine-grained changes would require very

careful individual analysis. Thus, at best, human neuroimaging is most likely to be sensitive to gross changes in spontaneous firing involving a spatially extensive population of neurons." The implications of animal measurements of temporal firing pattern and tonotopic reorganisation are also explained in terms of their application to human neuroimaging studies.

Secondly, at the start of the review where we make initial reference to the guiding principles from animal electrophysiological studies, we always provide some summary conclusion on its relevance to human neuroimaging studies of tinnitus. For example in the section 'Guiding principles from animal studies' on pages 5-7, when reporting the four caveats limiting the direct linkage between animal findings and human results we end each paragraph with the following new statements:

1) Thus, while noise trauma may provide a more appropriate model for TI in humans, its use in the laboratory is not so popular.
2) Thus, abnormal patterns of activity observed during the anaesthetised state may not be directly applicable to the awake state (either animals or humans).
3) While some conditioning paradigms can provide estimates of pitch and loudness (Jastreboff and Sasaki, 1994), a complete characterisation of the perceptual and psychological attributes of TI cannot be established in laboratory animals. One clear advantage of working with people is their ability to introspect and report on their own perceptions and feelings.
4) Thus, neural phenomena observed in the animal model may not always be detectable in humans using non-invasive neuroimaging methods.

While many of the important imaging studies are reviewed, the evaluations tend to be somewhat superficial. Comments are sometimes included about the imaging technique or the results, but it is sometimes difficult to judge the significance or relevance of the comments. The manuscript often contains experimental details (# of subjects) that seem to be unnecessary for a review paper.

We have now removed any experimental detail that is not important to the interpretation of the results. Sometimes the laterality of the TI percept was reported even when the results of the neuroimaging studies were not interpreted with respect to the TI laterality. In these cases, details of laterality of TI have been deleted.

We have also cast a more critical eye on each study and clarified the scientific relevance of our comments by adding further qualification at various points throughout the manuscript. For example on page 27 we say: "However, no data were reported for gamma-band activity and so this particular aspect of the model prediction was not tested". As a further example, on page 32 we say: "While 2 kHz corresponded to the edge of the hearing loss, the TI pitch was matched near the peak of hearing loss, not the lesion edge. Therefore, this result is not fully explained by the tonotopic reorganisation model of TI."

We also make general critical comments about the methodology, for example, regarding statistical power to make general conclusion from a small sample of data. On page 13 we say: "For any conclusion to have some diagnostic or predictive validity, sufficient statistical power is

required to support the inference that the mean effect over the population is significantly greater than under the null hypothesis. This typically requires a random-effect analysis in which the subject-to-subject response variability can be reliably estimated and for this the dataset should ideally include more than 20 subjects (Thirion et al., 2007). A majority of functional neuroimaging studies fail to reach such numbers and to illustrate this point, we highlight sample size throughout our review."

The manuscript could be improved by synthesis of prior imaging studies of tinnitus.

We have addressed this suggestion by emphasizing where appropriate what is the overall conclusion to be gained from the different investigations on one aspect of TI. For example, for the lidocaine studies on page 17 we say: "Thus, although the precise cortical locations of the sites of lidocaine action appear to vary across different reports, these results tend to confirm a pivotal role for extra-auditory cortex in the perception of TI, including regions engaged in multisensory integration and cognitive function." Other similar inclusions are inserted throughout the manuscript which are too many to list here.

The sections on animal electrophysiology do not really add much other than providing relevant references indicating that spontaneous rate can increase in many areas of the brain or that c-fos changes or that synchrony has been observed. Moreover, the review is incomplete by failing to mention all the studies by Kaltenbach in the dorsal cochlear nucleus. The Kaltenbach studies provide strong support for increased spontaneous rate in the dorsal cochlear nucleus, but these studies are not mentioned. The dorsal cochlear nucleus results are relevant to somatic tinnitus. There are problems with the dorsal cochlea nucleus model. For example spontaneous rates increase 4-7 days after cochlear insult, long after tinnitus might be expected to start based on Heffner's behavioral work. Including the c-fos studies in the electrophysiology section seems out of place. C-Fos measures the expression of a protein that may or may not be linked to the degree of neural activity. Rather than trying to review and summarize all the electrophysiological studies in a critical and comprehensive manner, it would make more sense to simply discuss the 3 general spontaneous activity models (p 8) of tinnitus.

This concern is partly dealt with in response to the first point regarding our review of the animal work. We have shortened these sections so that they are more focused on issues relevant to human neuroimaging studies. While animal studies of DCN activity have provided important insight into the mechanisms of tinnitus, DCN activity is barely detectable in humans by non-invasive imaging modalities. For this reason, animal studies of DCN are not reviewed. See page 20: "We do not provide a comprehensive review of studies that examine these cross-modal mechanisms because activity within the putative origin of this type of TI aetiology (namely dorsal cochlear nucleus) is barely detectable using human neuroimaging techniques. Instead we illustrate some of the neural changes that occur in higher centres of the auditory system that receive inputs from the dorsal cochlear nucleus."

The Conclusion, while pointing out some of the shortcomings of previous studies and potential opportunities for future research, offers little in the way of coherent summary of previous neuroimaging studies of tinnitus.

We have significantly revised the conclusion to clearly state the contribution of neuroimaging to tinnitus. On page 42 we state "The results of non-invasive human neuroimaging studies have validated the claim that TI is associated with changes in structure and function at various sites in the central auditory system. One of the significant contributions of human neuroimaging concerns its ability to define brain centres involved in the psychological aspects of the disorder, such as the limbic system. Further work to determine correlations between the amplitude of the response in these structures and the reported scores for TI annoyance will be important for corroborating a neurophysiological model of the TI network. Nevertheless, it remains a challenge to synthesise the current body of data into a set of firm conclusions regarding the key mechanisms underpinning TI within the auditory system."

In the remainder of the concluding section we concentrated on possible reasons for the challenges in synthesising the current body of data into a set of firm conclusions regarding the key mechanisms underpinning TI within the auditory system and suggest ways in which future imaging studies can improve on past methods.

Specific Comments

Abstract: This comment adds little and can be eliminated ".that has been so far derived primarily from animal research."

This sentence has now been removed

p. 3 Introduction: This number seems high and it is confusing since it is unclear if it is 20% of the population or 20% of those that experience tinnitus. Indicate the percent that seek medical treatment ".for about 20% ".

We have rewritten the sentence on page 3 so as to be clearer: "Tinnitus is prevalent in the general population, with approximately 10-15% of people experiencing it in some form. For about 20% of people experiencing tinnitus, it is sufficiently bothersome to seek treatment from their doctor or hearing specialist"

p. 8: The Gu et al 2008 citation is an abstract and should not be included in a review paper.

We have removed the reference to the Gu et al. conference report on page 8. However, if we remove all reference to the study reported by Gu et al. then there is no human neuroimaging evidence for the important contribution of hyperacusis to the hyperexcitability previously attributed to tinnitus alone. In the discussion on page 44 there is some brief mention of this with clarification that this was a conference report. "The importance of controlling for hyperacusis has been highlighted in a recent conference report demonstrating that the increase in neuronal

excitability to sounds in TI patients may be ascribed to hyperacusis rather than to a mechanism specifically related to TI (Gu et al., 2008)."

p. 12: The manuscript states "Compounds that are abundant in the body and have a short half life are typically used to measure functional activity". This is not entirely accurate. Some tracers are not abundant in the body, but are used because they target specific structures such as dopamine or dopamine receptor subtypes. For brain imaging studies, an important requirement is that the tracer must cross the blood brain barrier. Some tracers are exogenous drugs, such as benzodiazepine which bind to specific receptors in the brain.

We have now reworded this sentence on page 11 to read: "Various compounds that cross the blood brain barrier and have a short half life are typically used to measure functional activity."

p. 15: The Melcher et al. 2000 paper that is widely cited has not been replicated by the author or other labs. One reason for this is that the magnitude of a sound evoked response may be affected by hyperacusis as well as tinnitus.

We have added sentence to refer to the possibility of hyperacusis affecting the results and say the following on page 14: "Within this model it is also plausible that hyperacusis leading to an abnormally large response to external sounds may also partly explain the limits on overall activity in patients with TI."

p. 18: "rTMS..principles of electromagnetism to inhibit neural activity by.". This explanation seems overly simplistic. The magnetic field passing through the skull creates a transient current flux with a complex entry and exit pattern that may both excite and inhibit neurons. Stating that it "inhibits neural activity" only makes little sense.

The precise mechanism by which TMS suppresses tinnitus is unknown. We have changed the word inhibit to "alter" on page 19.

p. 18-20: Much of this section is devoted to rTMS studies that are mainly related to tinnitus, but not particularly relevant to brain imaging of tinnitus. A good deal of this could be eliminated.

We have done as suggested and significantly shortened this section. We have added the following sentence on page 19 to point out the significance of TMS for neuroimaging: "When TI co-occurs with a hearing loss, it is not possible to clearly attribute the abnormal activity to TI. However, if the subsequent rTMS applied to the site of maximal TI-related activity is successful in reducing TI, then this finding increases confidence that this cortical site plays a causal role in TI."
We provide only two examples of this approach (Plewnia et al., 2007 and de Ridder et al., 2004). We conclude this section on page 20 by saying "Although requiring replication, these two rTMS studies point to the essential role of auditory cortex and regions of multisensory integration in the perception of TI."

p. 21. "Two PET studies are worth mentioning here. Cacace et al. (1999) reported that one patient with left-sided deafness following neurosurgery was able to elicit left-sided TI by performing repetitive finger-thumb opposition tapping movement with the right hand." This statement is incorrect; the Cacace study utilized fMRI not PET to identify patterns of activity.

We have now corrected this mistake on page 21.

p. 24: "A link between the constancy of the TI percept and coincidence across neurons of their ongoing spontaneous spiking activity is taken as evidence for a direct relationship between the perceptual and neural phenomena." This statement is not particularly clear or entirely accurate. Many regions of the brain show coherence in their neural activity firing patterns, but coherence per se may not be sufficient to generate tinnitus if the coherence occurs in nonauditory areas.

We have now removed this sentence from the manuscript.

p. 24: The text mentions figures 3c & 3d, but these figures were not present and the Figure legend does not mention the figures.

This should be Figures 2c & 2d which we have now corrected.

p. 26: There is not need for explaining the obvious "Hyperpolarisation describes a change in membrane potential that makes it more negative (less positive)."

We have now removed this sentence.

p. 27: This whole section deals with oscillatory circuits in the cortex, but then suddenly jumps to auditory nerve fiber data in the cat to invoke the edge model of tinnitus "This led some investigators to speculate that tinnitus was not the result of increased spontaneous activity per se but rather a neural "edge effect" produced by contrasting cochlear regions having normal and low levels of activity (Liberman and Kiang, 1978)." It is not necessary to invoke the auditory nerve here.

We have removed the reference to auditory nerve data and rewritten the previous sentence on page 26-27: “Llinas et al. (2005) speculate that tinnitus is not the result of increased spontaneous activity per se. Rather, TI is considered to be a neural "edge effect" that originates in the cochlea at the point of contrasting ‘normal’ and ‘low’ levels of activity and is transmitted throughout tonotopic regions of the ascending central auditory system.”

p. 42: "..while sounds typically engage activate this network, a tone." delete activate.

The word ‘activate’ has been deleted.

p. 43: "one octaves." change to singular, octave.

This correction has been made.

p. 43: "Langers and Melcher (2008)"; conference reports do not belong in review papers since there is no way to independently evaluate what was reported and since the final results may differ from what was presented at the conference.

We have removed this paragraph on page 41 and replaced it with the brief sentence: “However, to date we could find only one unpublished report of this approach (Langers and Melcher, 2008 conference report).”

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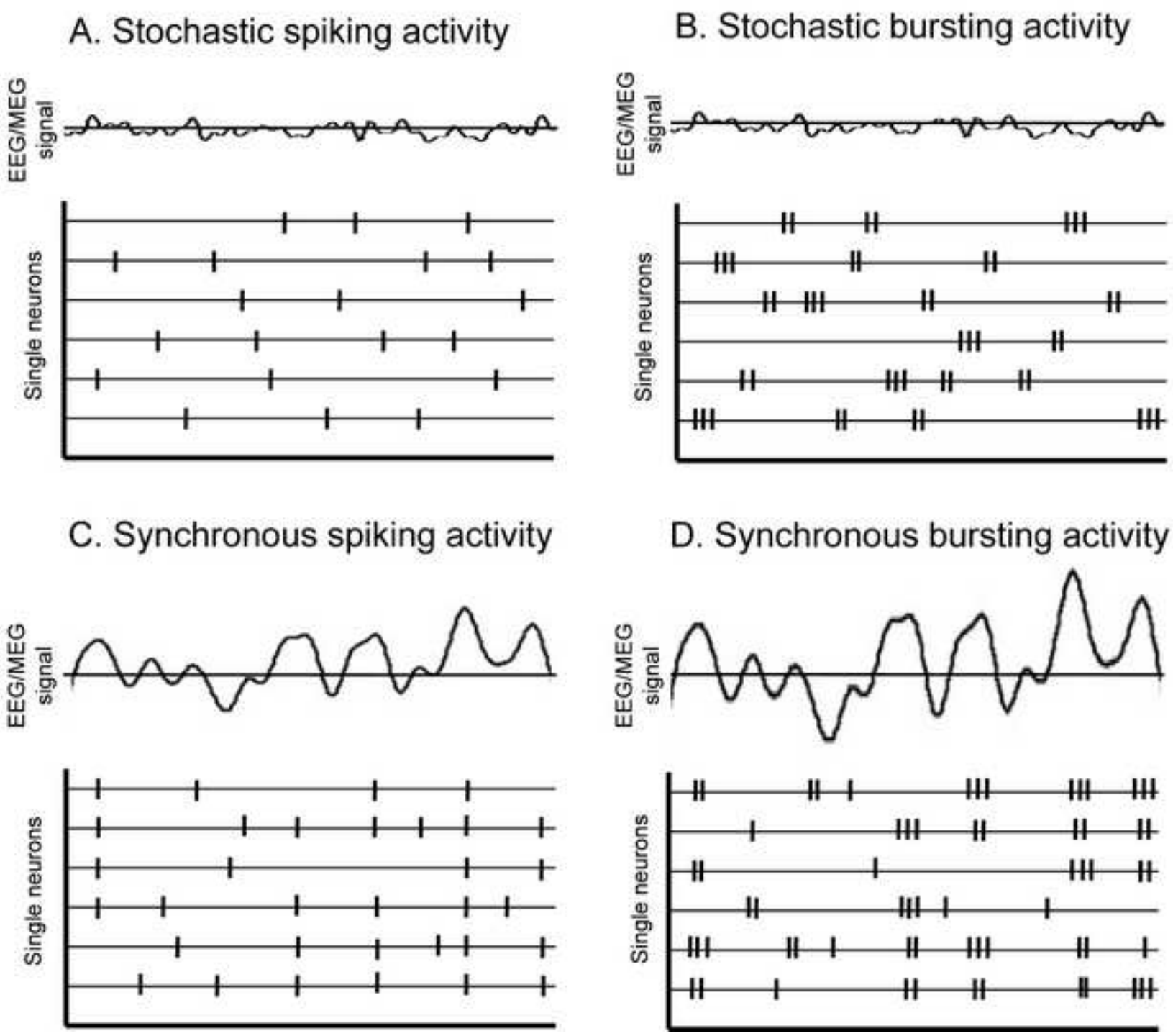

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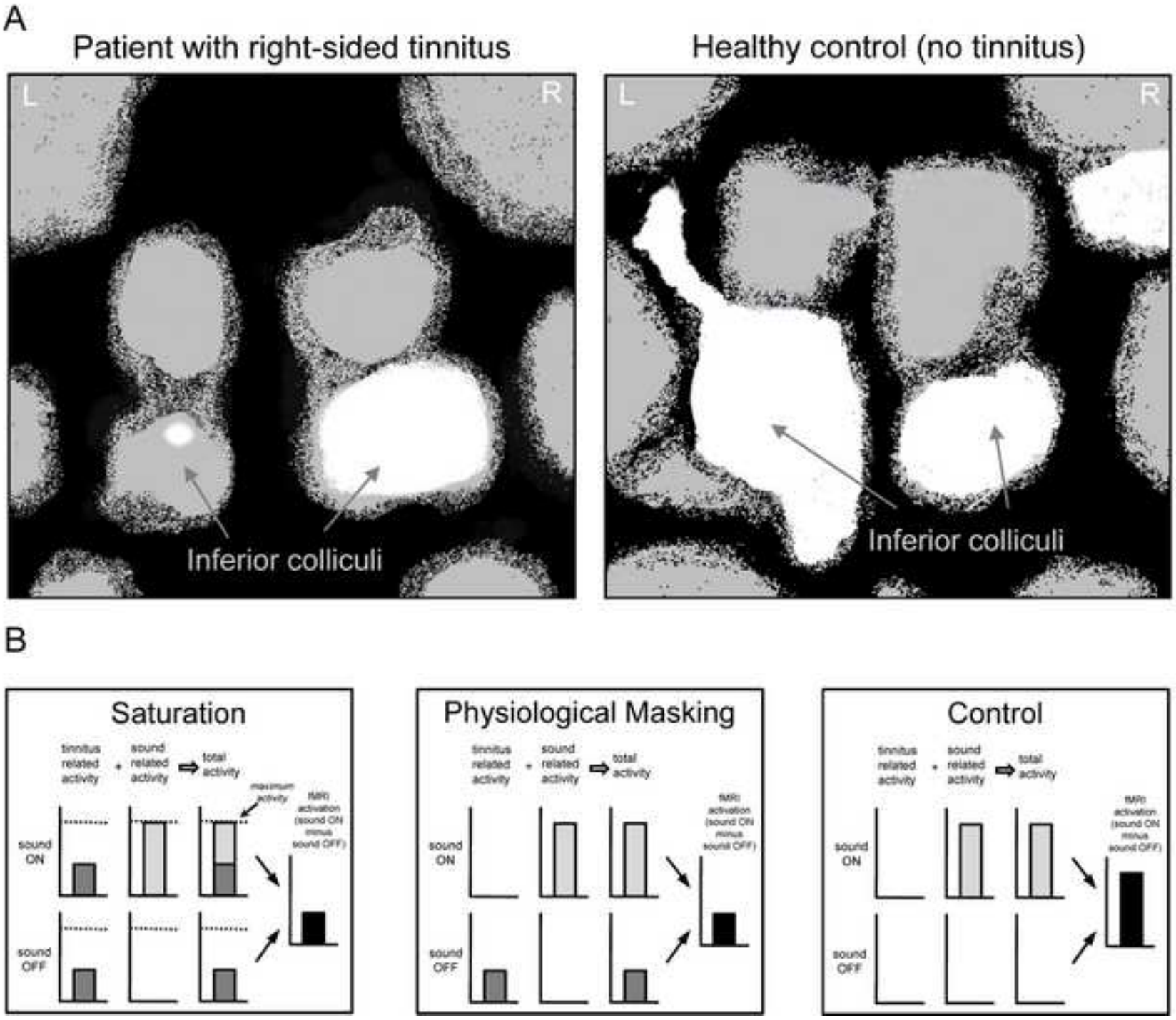

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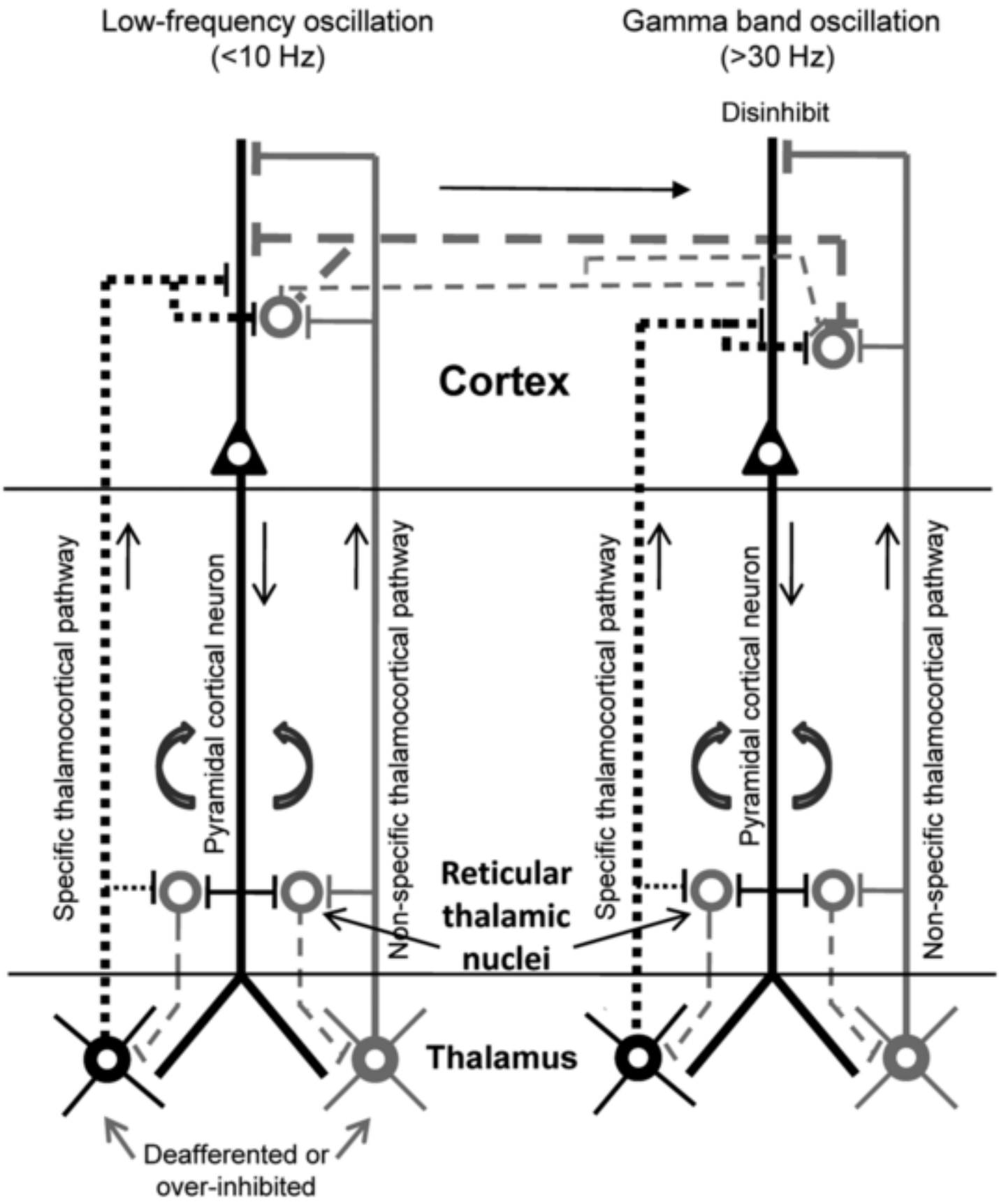

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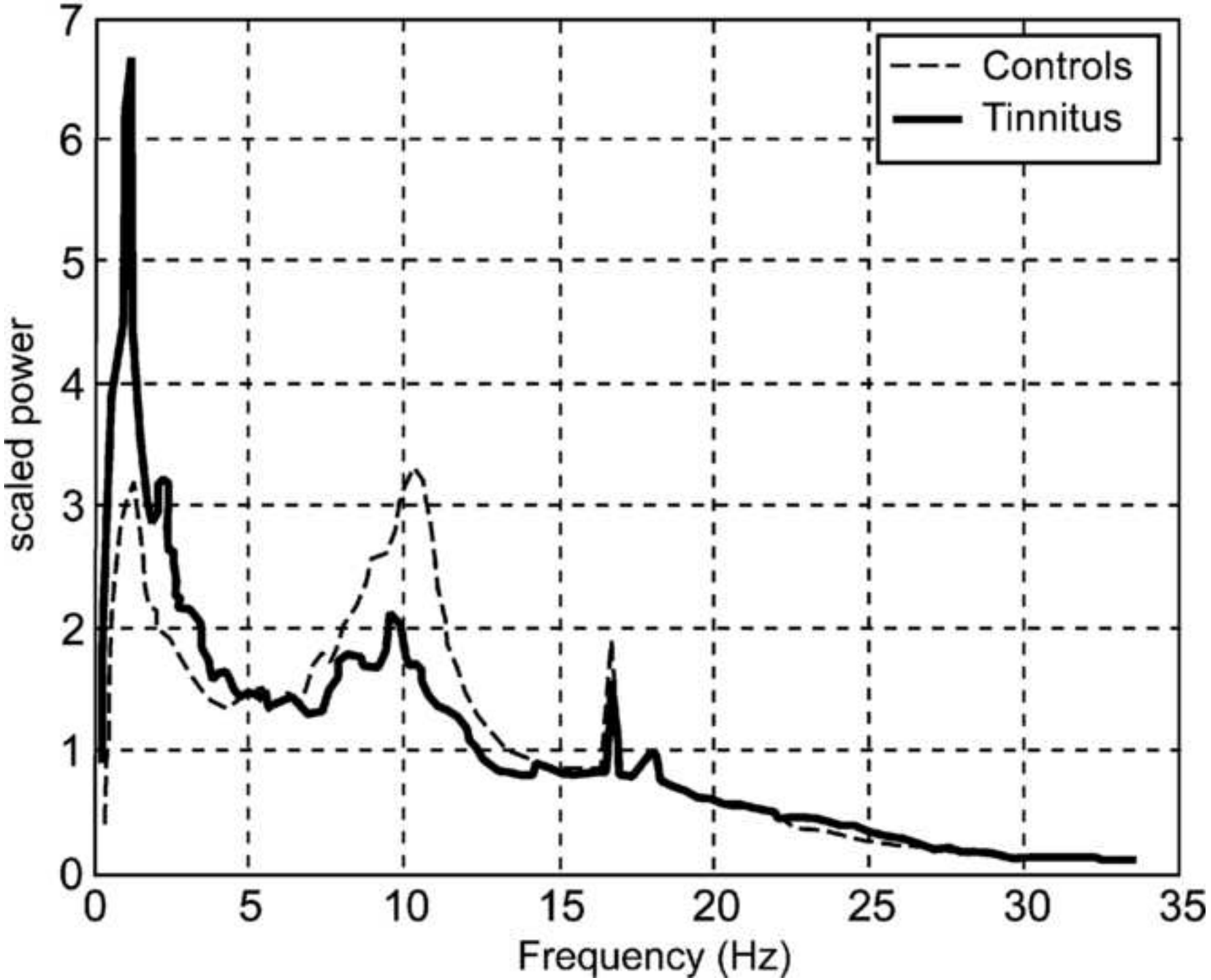

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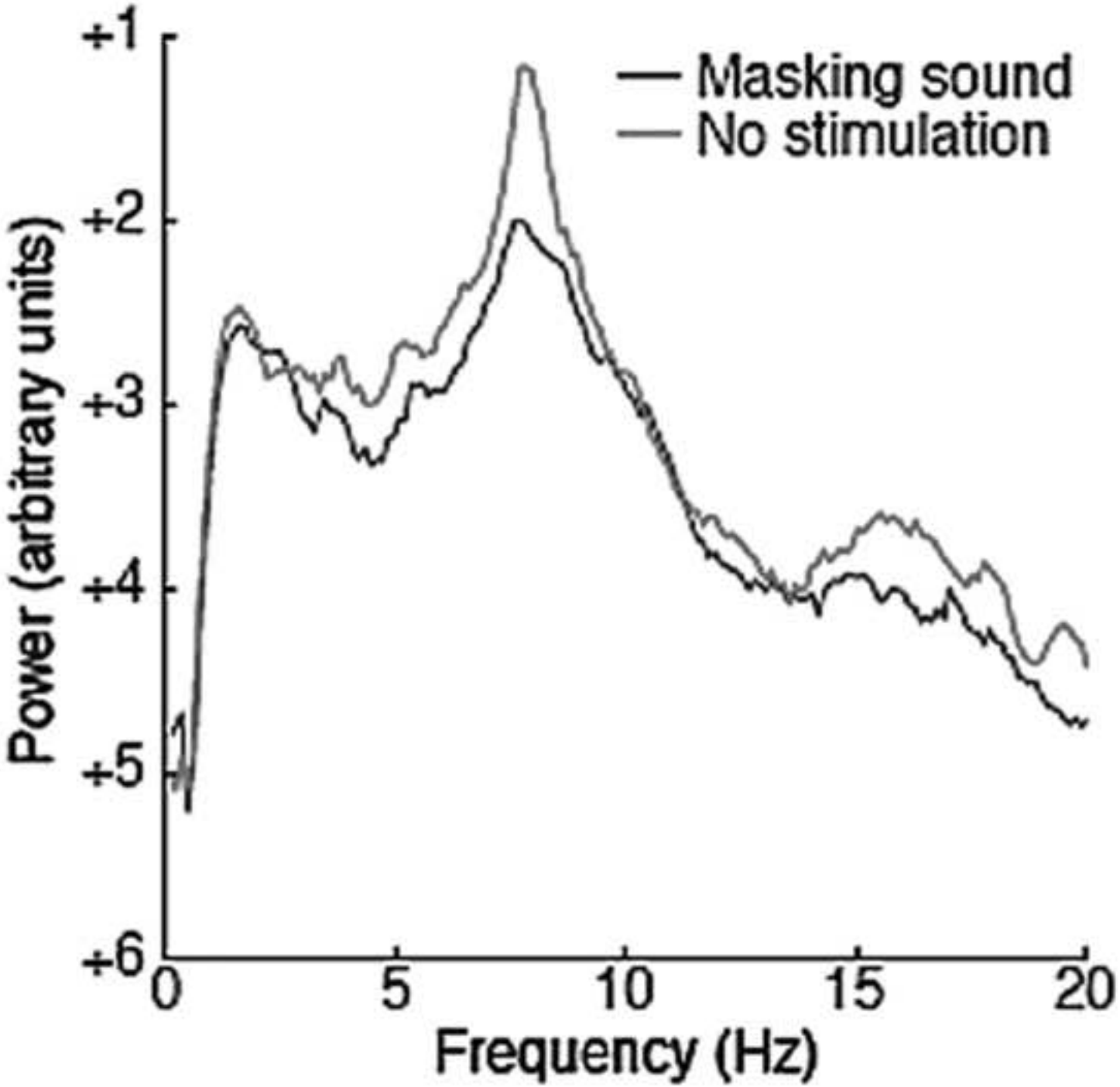

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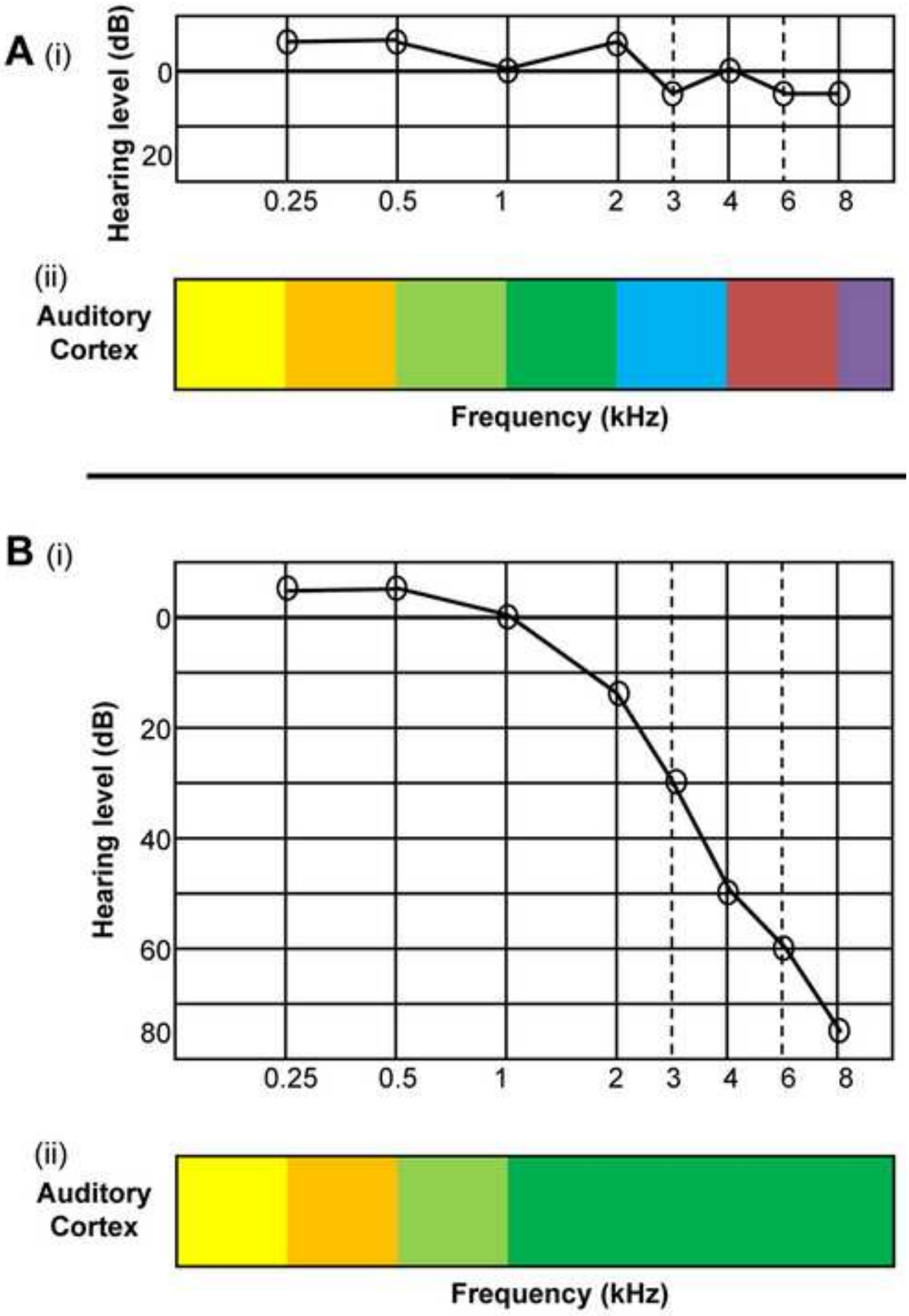

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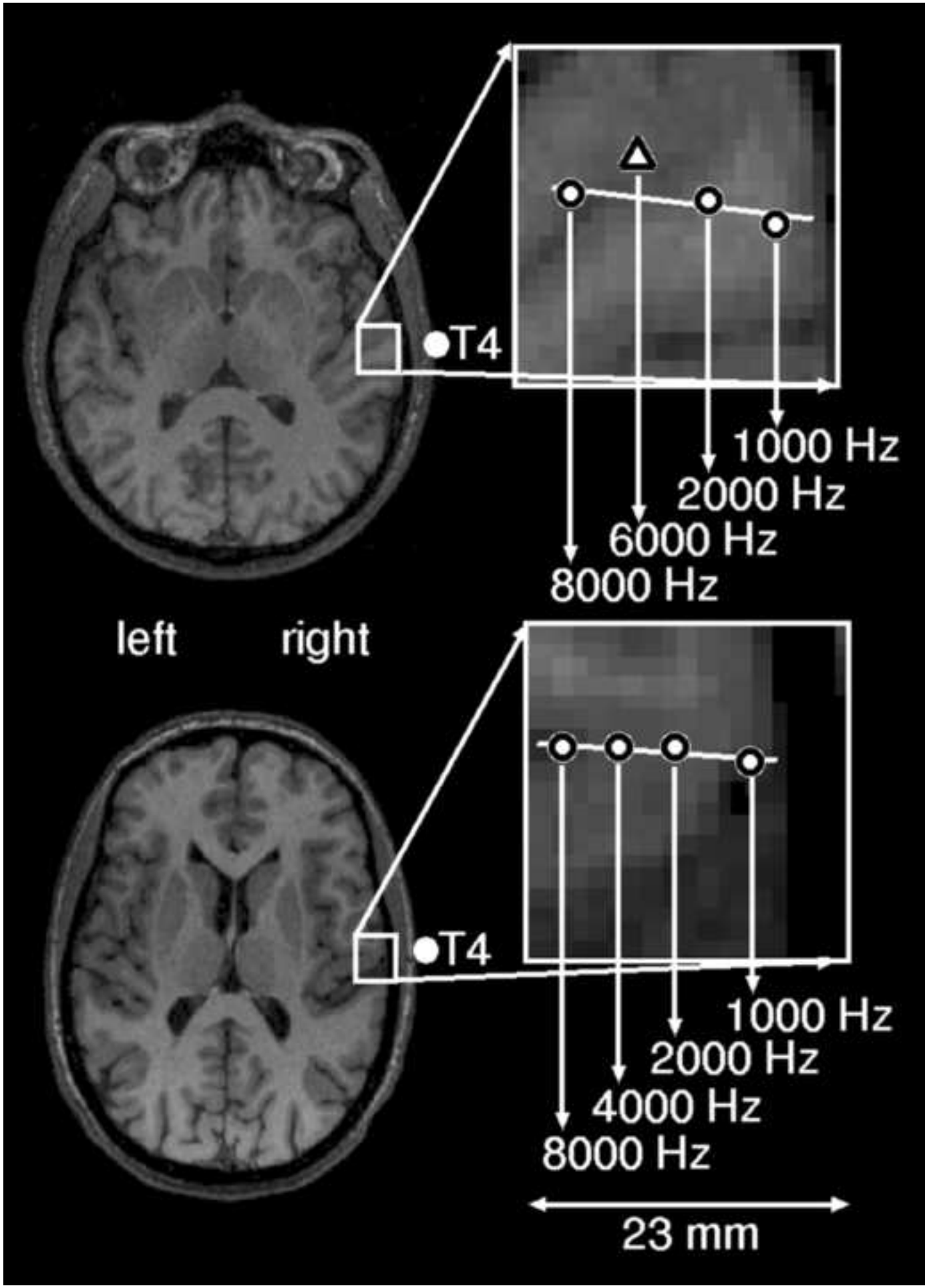

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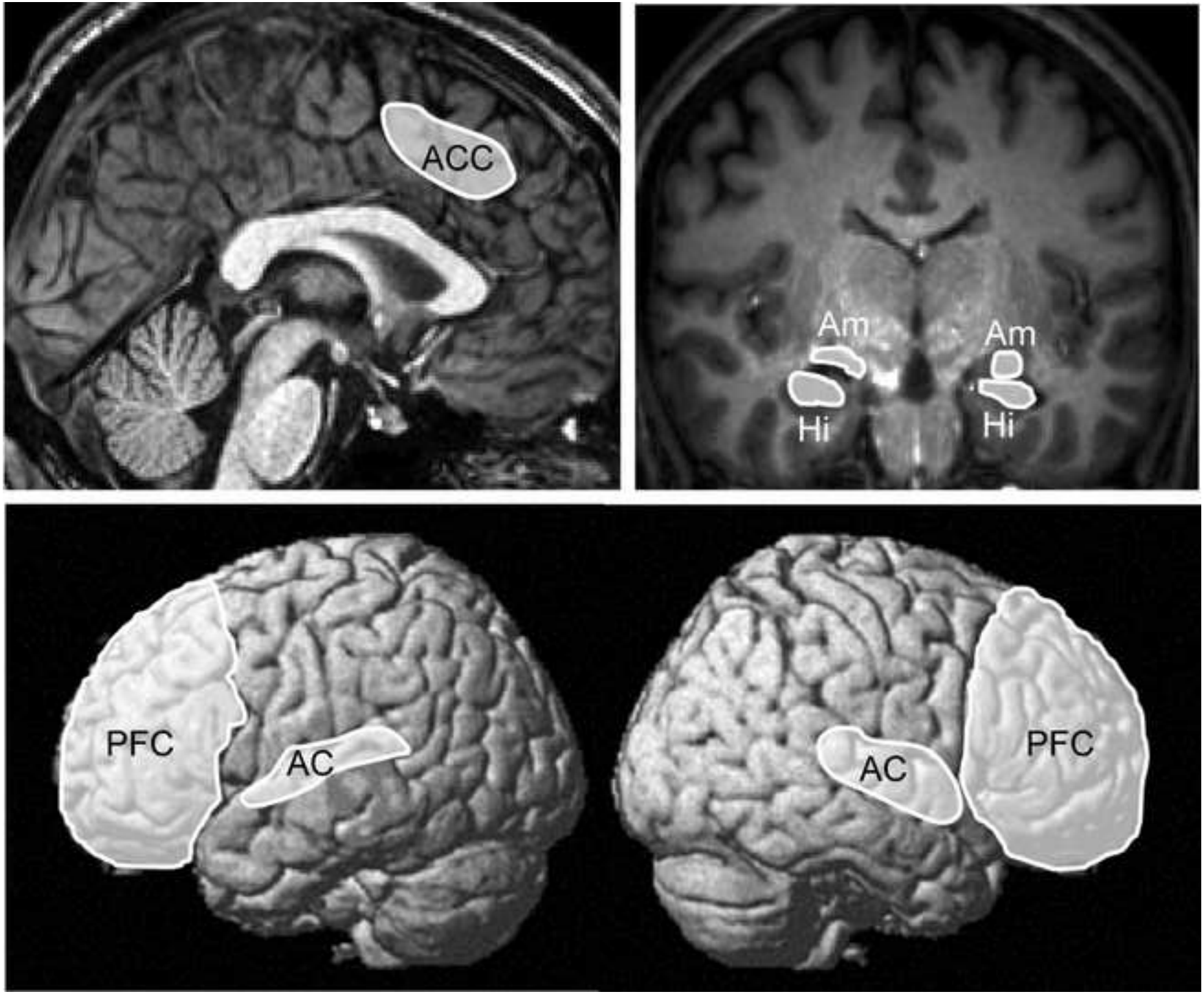

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