RESIDUAL INHIBITION, HEARING LOSS AND TINNITUS

RESIDUAL INHIBITION, HEARING LOSS AND THE NEURAL BASIS OF TINNITUS

By

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ABSTRACT: The phenomenon of residual inhibition, whereby the phantom sensation of tinnitus is suppressed following the presentation of a masking stimulus, has significant implications for understanding the neural basis of tinnitus itself. By using novel psychoacoustic techniques and three computer-based tools developed and applied specifically to measure tinnitus sensation and residual inhibition, a pattern emerges in which the depth and duration of tinnitus suppression relates to the center frequency of the band-passed noise masking stimulus. A correspondence between the region of hearing loss, the tinnitus spectrum and the masking stimuli most effective in suppressing tinnitus is revealed. These results suggest that cortical reorganization observed in animal models of tinnitus is not the principal basis of tinnitus, and provide a baseline for optimizing residual inhibition in individual cases and for further experiments.

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INTRODUCTION

Tinnitus is a phantom auditory sensation defined as the perception of sound in the absence of an acoustic stimulus. Most tinnitus sufferers describe a high pitched "ringing" or "hissing" sound, located in the ears or the head (Henry & Meikle 2000) as their subjective experience of this disorder. Though such characterizations of the tinnitus percept are based on subjective report, they have informed both neuroscience research and clinical approaches to the disorder. Nevertheless, more detailed psychoacoustic data addressing both tinnitus and its suppression would be of value to the field.

An understanding of tinnitus is of interest for two principal reasons. First, approximately 10% of the North American population experiences tinnitus, while 1% reports their quality of life adversely affected by the condition (Lockwood et al. 2002). There are currently no effective pharmacological treatments and only a very few psychoacoustic treatments that give temporary relief (Langguth et al. 2006a) for chronic, disturbing tinnitus. Any insight into the psychoacoustic characteristics of tinnitus may further inform efforts to develop effective means of tinnitus remediation. Second, insight into these same psychoacoustic characteristics may shed light on properties underlying the function of the auditory system under abnormal (ie. tinnitus) conditions and, by extension, under normal conditions.

Tinnitus can be suppressed for brief periods on the order of seconds to minutes after acoustic masking (Henry & Meikle 2000). This phenomenon is known as "residual inhibition" in the tinnitus literature. Residual inhibition is poorly characterized with respect to the properties of the tinnitus sensation among individual tinnitus sufferers. Psychoacoustic techniques have the potential to elucidate the relationship between properties of the tinnitus sensation, residual inhibition, and the function of the auditory system.

This thesis describes several novel psychoacoustic tools for measuring tinnitus and residual inhibition and presents data from a cohort of tinnitus sufferers assessed using these techniques and traditional audiometry. I begin by reviewing evidence regarding the neural mechanisms underlying tinnitus. Then I consider implications for the psychoacoustic properties of tinnitus and RI, before turning to the current study.

THE MECHANISM OF TINNITUS

The history of tinnitus research mirrors, in many respects, the revolutions undergone by many other branches of perception research. Initially focused on physical attributes of stimuli and sensory epithelial processing, the field gradually shifted focus (Henry & Meikle 2000) to the peripheral neural correlates and more

recently to central and cortical mechanisms (Eggermont & Roberts 2004). Tinnitus is often accompanied by hearing impairment measured by the clinical audiogram, which typically assesses hearing thresholds for sound frequencies up to 8 kHz. Though it is widely believed that sensorineural hearing loss expressed in the audiogram is an essential step preceding the onset of tinnitus, detection of hearing deficits in all tinnitus sufferers has eluded previous studies.

Early tinnitus theorists, relying largely on patient reports of acoustic trauma, hypothesized that tinnitus had a cochlear origin,, implicating hair cells in the pathophysiology of the disorder. Zenner and Ernst (1993) propose a model of inner hair cell dysfunction involving "leaky" synapses that result in excess stimulation of auditory neurons, while others (Kaltenbach 2000, Norton et al. 1990) propose outer hair cells as the culprit, citing evidence from studies of spontaneous otoacoustic emissions and their correspondence to the tinnitus percept.

Baguley et al. (2006) demonstrated a correspondence between compression of the eighth (auditory) nerve, particularly in cases of acoustic neuroma and the development of tinnitus. In fact, tinnitus is an important flag for clinicians in the diagnosis of acoustic neuroma, and it likely shares much of the same neuronal etiology as tinnitus from other causes.

Zhang & Kaltenbach (1998) and Salvi et al. (1983) found an increase in the spontaneous firing rates of neurons in dorsal cochlear nucleus (DCN) and inferior colliculus (IC) after noise trauma, implicating both of these structures in the pathophysiology of tinnitus. Interpreted in light of Gerken's (1984) work on EEG in cats under similar conditions, which showed simultaneous, correlated decreases in electrical stimulation thresholds in DCN and IC, it is likely that IC acts as a relay station for hyperactivity in the DCN (Kaltenbach 2000)

While little is understood of the role of auditory thalamus (medial geniculate body, MGN) in tinnitus, the work of Eggermont and colleagues in animals has pointed to auditory cortex (AC) as one center of neural activity underlying tinnitus and related phenomena. Cortical map reorganization in cats after acute noise trauma, in which high frequency-tuned neurons were shown to shift their tuning curves to those of lower adjacent frequencies (Norena & Eggermont 2003), was initially thought to correspond to the development of tinnitus, in accordance with Rauschecker's hypothesis (1999) of tinnitus as an audiometric edge phenomenon. In Rauschecker's model, tinnitus arises at or just above the frequencies at which normal hearing thresholds become abnormal. Norena & Eggermont (2003) postulated that this map reorganization arises from an unmasking of normally silent diverging thalamocortical projections from the auditory thalamus when lateral or feedforward inhibition is diminished in the cortex following hearing loss.

Cortical reorganization as a potential cause of tinnitus was given further credence by the work of Weinbruch et al. (2006) in human subjects, who showed with MEG both a degraded tonotopic organization and a greater dipole moment in tinnitus sufferers as compared to controls. Functional brain imaging data suggest that the anatomical seat of this phantom percept lies not in the auditory periphery or early auditory pathway, but in a network of brain regions including the thalamus (Muhlau et al. 2006), auditory cortex (Lockwood et al. 1998, Seki & Eggermont 2003, Norena & Eggermont 2003) and/or extra-auditory structures in the basal forebrain and limbic system (Lockwood et al. 1998, Mahlke &Wallhausser-Franke 2004).

Recently, however, questions have been raised (Eggermont & Roberts 2004) as to whether cortical map reorganization underlies the tinnitus sensation or is instead an epiphenomenon. Eggermont & Norena (2003) point out that while hyperactivity in DCN develops several days after noise trauma, and in auditory cortex several hours after the same, the percept of tinnitus in humans sets in nearly immediately after noise exposure, suggesting that a mechanism related to but other than the above-mentioned tonotopic map reorganization may in fact be the cause of tinnitus. Eggermont & Roberts (2004) described an alternative tinnitus mechanism in which increased neural synchrony within central auditory structures affected by hearing loss may be the principal cause of the tinnitus

percept. While increased cross-correlated neural activity within AC (Seki & Eggermont 2003, Norena & Eggermont 2003) may alone be responsible, MEG data from Llinas et al. (2005) showing increased power in the theta band (4-8 Hz), and Weisz et al. (2005) showing increases in delta (1.5-4 Hz) and a reduction in alpha (8-12 Hz) band power, suggest the involvement of an oscillatory circuit. To explain these changes in the EEG power spectrum, Llinas et al. (2005) propose that disinhibition arises from deafferentation in central auditory structures. This disinhibition leads, in turn, to an increase in spontaneous neural synchrony in the form of a thalamocortical oscillatory loop.

The hypothesis that tinnitus reflects hypersynchrony in regions of the auditory system affected by hearing impairment makes predictions about the spectral properties of tinnitus. This hypothesis also suggests a mechanism for residual inhibition (desynchronization). If these hypotheses are correct, we would expect tinnitus spectra to span the region of hearing impairment in tinnitus sufferers. Sounds that induce residual inhibition (RI) should optimally span this region as well. Study of these psychoacoustic properties is therefore relevant to understanding the mechanism of tinnitus as well as the basis of RI.

PSYCHOACOUTSIC PROPERTIES OF TINNITUS & RESIDUAL INHIBITION

Psychophysical measurement of tinnitus, given the disorder's subjective nature, is anything but easy. In the absence of expert musician or acoustician tinnitus sufferers, who might be capable of characterizing their percepts in an insightful and quantitative manner, experimenters must resort to a mixture of traditional and novel sensation matching techniques to approximate tinnitus in terms of real acoustic stimuli.

Quantitative characterization of the tinnitus percept began as early as 1821, when it was recognized that different "types" of tinnitus were masked more or less effectively by sounds of different pitch. It was not until 1931 that a thorough characterization of the dimensions of tinnitus percepts was attempted (reviewed in Henry & Meikle 2000). In the earliest experiments, Wegel (1931) and Josephson (1931) independently matched subjects' tinnitus sounds in both loudness and pitch using pure tones.

Loudness recruitment, a psychoacoustic phenomenon whereby subjects with elevated auditory thresholds experience a steeper-than-normal relation between perceived and actual changes in stimulus intensity, may have played a role in confounding early attempts at tinnitus characterization. Fowler (1950)

expanded Wegel's and Josephson's work in demonstrating the phenomenon of loudness recruitment in tinnitus patients, despite never actually employing the concept of recruitment in his analysis. Both Fowler (1950) and Goodhill (1952) noted patients' difficulty in characterizing their tinnitus and ascribed this problem to unfamiliarity with psychoacoustic dimensions and pure-tone stimuli. Goodhill may have been the first to use randomized presentation of a range of stimuli in matching the tinnitus pitch.

The first large-scale psychoacoustic study of tinnitus, undertaken by Reed (1960) was also the first to introduce the dimension of bandwidth to the field, incorporating it alongside loudness and pitch. In addition to this important innovation, Reed's work was also the first to dissociate the emotional and psychological impact of tinnitus on patients' lives from the perceptual properties of the condition, when he found no correlation between tinnitus severity and any of the three physical stimulus dimensions of loudness, pitch and duration. Following this significant revelation, Graham and Newby (1962) demonstrated the importance of robust psychophysical characterization in understanding tinnitus by demonstrating no correspondence between the psychoacoustic properties of tinnitus and their subjects' qualitative descriptions.

Few (if any) novel approaches to tinnitus sensation matching had been tried in the wake of Reed's work, until Norena et al. (2002). Norena et al.

examined the relation between tinnitus pitch and audiometric threshold shift by producing an "internal tinnitus spectrum" for subjects that did not require a single best-match approach. Instead, subjects were asked to rate each of several independently presented pure tones for the extent to which the tones resembled the subject's tinnitus sensation. This approach accommodated subjects with more complex tinnitus sensations.

In addition to his early contributions to pitch matching of tinnitus, Wegel (1931) may also have been the earliest to quantify tinnitus masking. He did so by plotting a minimum masking level (the smallest sound level at which tinnitus masking is achieved) curve for multiple pure tone stimuli. Not until the advent of Feldmann's (1971) work, which demonstrated a range of previously uncharacterized masking phenomena, were psychoacoustic attributes of tinnitus rigourously evaluated again.

Only a very few (Henry & Meikle 2000) studies of the psychoacoustic parameters of masking have been undertaken. Feldmann's work (1971, 1983) is one of the most comprehensive, covering the frequency dependence of masking, minimum masking levels, laterality of masker presentation and the influence of hearing loss. Feldmann showed that different bandwidths of masking sounds could produce characteristic patterns based on the stimulus level required to mask tinnitus, and used these patterns to divide tinnitus into five types based on the

masking behaviour. He also demonstrated that the duration of residual inhibition varied with the intensity, but not the frequency, of the masking stimulus. More important, however, was Feldmann's discovery that residual inhibition could be generated via masker presentation to the ear contralateral to tinnitus, and his deduction that the mechanism of RI, and thus the mechanism of tinnitus, resides in central structures within the auditory system.

Results of the studies above provide some important clues in designing psychometric procedures for assessing tinnitus. It appears that in early psychoacoustic studies tinnitus of types other than a single pure tone were often neglected. This oversight is particularly significant given that up to 46 percent of sufferers experience a tinnitus consisting of more than one sound (Henry & Meikle 2000). Furthermore, inexperienced subjects may have difficulty distinguishing the dimensions of pitch, loudness and bandwith, especially when attempting to integrate these concepts as they apply to novel acoustic stimuli, and even more so when asked to compare these dimensions to their subjective percept. Vernon & Meikle (1981) advise a systematic approach, first matching loudness and then pitch.

Tinnitus loudness matches fall, for more than 80 percent of subjects measured by prior means, at levels below 10 dB SL (above hearing threshold) at or near the tinnitus frequency (Goodwin & Johnson 1980, Tyler & Conrad-Armes

1983). When matched to sounds well below the frequency range of the tinnitus percept, loudness judgments are substantially higher (Henry & Meikle 2000) in sensation level. Relatively low loudness matches in the region of tinnitus frequencies suggest recruitment at these frequencies. Penner (1984) notes that tinnitus loudness matches in dB SL are essentially inverse functions of absolute hearing thresholds, and can be considered as iso-loudness contours in subjects with loudness recruitment. He advocated the use of sones as a more accurate reflection of perceived tinnitus loudness. Meikle et al. (1995) report similar functions, and note that these "loudness matching curves" can be fitted relatively well using linear regression for 80 percent of subjects.

Vernon's results and his own recommendations (reviewed in Henry & Meikle 2000) suggest three important protocols in loudness matching. First, stimuli must be presented in ascending order from below threshold to avoid masking the tinnitus or producing residual inhibition; second, increments of loudness should be approximately 1 dB; third, that hearing threshold should be measured in the same experiment to avoid "spurious differences" between threshold and loudness match introduced by variance in threshold measures.

Matching the pitch of tinnitus may present a more difficult problem than that of loudness, but it also offers more clues as to the neural basis of tinnitus. Nearly all previous studies of pitch attempted to match tinnitus using pure tones

in a two-alternative forced choice presentation, proceeding either in either continuous stepwise increments, between successively narrowing increments, or some combination of the two (Henry et al. 2001). While these methods provide relatively good insight into the relationship between tinnitus and audiometric threshold shift, endpoint frequencies appeared to depend on the order of stimulus presentation and the frequency step size between trials (Henry et al. 2001). Worse still, these approaches did not resolve the problem of "octave confusion" whereby some subjects match their tinnitus to objective stimuli at octave intervals above or below the frequency of the percept. Within subject test-retest reliability for this approach is relatively poor (Tyler & Conrad-Armes 1983, Norton et al. 1990).

Noting that this cross-session variability might arise because many subjects experience some tinnitus percept other than a single pure tone, Norena et al. (2002) demonstrate a novel approach to pitch matching in which subjects were asked to characterize whether each of a series of pseudo-randomly presented tones were present in their tinnitus percept, and further characterize each present component according to its contribution to the overall percept. Their assumption, however, remained a tinnitus percept that consisted of multiple tonal components, and this weakness was acknowledged by the authors.

Norena et al. (2002) showed a robust correspondence in the frequency domain between pitch "contribution" and auditory threshold shift, with regions of

audiometric deficit overlapped by the high ratings for tinnitus pitch, in both cases of notched audiograms and more standard presbycusic thresholds. Additionally, subjects showed maximal frequency discrimination thresholds (after log-scale correction) corresponding to frequencies of maximal hearing loss – essentially, elevated Weber fractions matching the tinnitus frequency. This was not, however, what these experimenters expected. Instead, their work had been based on the hypothesis first proposed by Rauschecker et al. (1999), and Norena et al. (2002) found not the expected preponderance of audiometric edge frequencies corresponding to the tinnitus pitch, but instead a broad span of the entire frequency range of threshold shift. Eggermont & Roberts (2004) proposed an alternative interpretation of the data of Norena et al., in conjunction with Eggermont's previous work on elevated spontaneous firing, of a disinhibition-driven increase in neural synchrony across the frequency region of hearing loss (rather than at the edge) underlying the tinnitus percept.

While the results of Norena et al. make a strong case linking hearing deficits and tinnitus, his relatively small sample of ten subjects leaves open the possibility of tinnitus sufferers with no measurable hearing deficits, as some researchers report anecdotally. One possible explanation for such cases is that hearing loss may be present outside the range of standard audiometry, and that high-frequency or high-resolution measures of threshold shift would uncover otherwise undetectable hearing deficits.

While Norena et al.'s results provide the most compelling evidence yet of a common etiology for hearing loss and tinnitus, a lower within- and cross-session variability than previous methods, and the first psychoacoustic data to rebut Rauschecker's hypothesis (1999) of tinnitus as an audiometric edge effect, they do not directly address the distinction between tonotopic reorganization and abnormal synchrony/ spontaneous firing as likely causes of tinnitus. Studies of masking and residual inhibition in relation to the tinnitus percept could inform this issue. Both phenomena would be expected to be expressed in frequency regions affected by hearing loss, where increased synchrony has been documented by animal studies (Eggermont and Roberts, 2004).

Compared to other psychoacoustic dimensions of tinnitus, masking has not been very thoroughly examined and residual inhibition (RI) even less so. Henry & Meikle (2000) note that tinnitus sufferers have difficulty tolerating pure tone maskers and most previous studies therefore employed narrow- to broad-band noise stimuli. They further note that despite several efforts to explore bandwidth and frequency dependence of masking, tinnitus masking is categorically different from conventional acoustic masking, with no discernible critical masking bandwidth, a high degree of between-subject variability, and the potentially counterintuitive observation that band-limited stimuli were often more effective maskers than broadband noise.

Feldmann's pioneering work on parameters of tinnitus masking remains an authoritative treatise; he noted that 90 percent of tinnitus sufferers experience some residual inhibition (Feldmann 1971). Despite the high prevalence of this phenomenon, substantial between-subject variability in RI duration is noted by Feldmann and others (Meikle et al. 1996, Terry et al. 1983) with most subjects reporting a duration less than one minute, and a very few reporting durations greater than ten minutes.

Although Terry et al. (1983) report a dependence of RI on masker centre frequency for narrow-band stimuli, their data suggest that frequencies well below tinnitus pitch matches were most effective, and neither Feldmann (1971, 1983) nor Tyler et al. (1984) show comparable frequency dependence. Despite this inconsistency, Terry et al. and Feldmann both show differences in RI duration proportional to the logarithm of masker duration, while Tyler et al. and Terry et al. show a dependence of RI duration on the intensity of the masking stimuli. Furthermore, Feldmann notes (1971) a robust, dichotomous effect between complete and incomplete tinnitus masking: without complete masking, RI is not present.

THE CURRENT STUDY

The following describes an experiment undertaken to elucidate the frequency dependence of the phenomenon of residual inhibition, of the tinnitus percept and of hearing deficits, and to examine the relationship between these three dependent variables in detail.

On the next pages, methods and data from this experiment are included in the form in which it was published in *Acta Otolaryngologica*. Following that, the discussion is expanded to detail further implications of the data on neural models of tinnitus, clinical treatments for tinnitus, and future research.

Pages 17-23 in this thesis were replaced with the citation below due to copyright issues.

Larry E. Roberts, Graeme Moffat & Daniel J. Bosnyak (2006) Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift, Acta Oto-Laryngologica, 126:sup556, 27-33, DOI: 10.1080/03655230600895358

DISCUSSION

Of our results, the primary emergent pattern is the expected one of a correspondence between the frequency dependence of the tinnitus pitch spectrum, residual inhibition depth, and the pattern of high-frequency threshold shift. Sounds judged to most closely resemble the tinnitus sensation were not limited to the edge of hearing loss but spanned the region of hearing impairment in the audiogram. Masking sounds in this region also produced the deepest and most long-lasting RI. Taken together, the results are consistent with the hypothesis that hypersynchrony occurring in the cortical regions affected by hearing loss is the source of tinnitus, and that segregation of this synchronous activity lasting on the order of 15-30 seconds is the mechanism of RI.

HEARING LOSS & AUDITORY THRESHOLDS

Figure 1A, showing high-frequency hearing loss, demonstrates a clear emergence of standard presbycusic hearing loss in most subjects. Although one might expect a group average to exhibit this pattern, it is of particular interest that all subjects exhibited some hearing loss at frequencies <16 kHz. While this finding is not surprising, it is noteworthy that some subjects showed no clinically significant hearing loss (that is, at frequencies <8 kHz). The emergence of deficits

only at high frequencies among clinically normal tinnitus sufferers is a novel finding.

Considered alongside the results of Weisz et al (2006), showing that clinically normal hearing subjects exhibit cochlear dead regions when tested for off-frequency listening, this high-frequency hearing loss suggests that previous results (Henry & Meikle 2000) showing tinnitus in clinically "normal" subjects may have been the result of incomplete measures of auditory function. The findings also suggest that deafferentation-driven plasticity arising from auditory deficits in the periphery may be an essential precondition for the development of tinnitus. Evidence from this experiment does not conclusively show such a relationship, but does, in conjunction with the results of Weisz et al., serve to steer consensus further.

Although this experiment did not attempt to address the issue of control subjects without tinnitus, as few of the measures described could be applied to subjects with no experience of tinnitus, recent evidence suggests that an age-matched control group may enable a further interpretation of the audiometric results. Konig et al. (2006) found that while tinnitus sufferers showed less overall threshold shift at high frequencies versus patients with noise-induced hearing loss

but no tinnitus, they showed a greater maximum slope in the audiogram at the edge of hearing impairment. These results lend some credence to the "audiometric edge" theory of tinnitus, and challenge the hypothesis underlying this experiment and that of Norena et al. (2002). The audiometric data reported herein could be extended by the addition of a control group to explore this question and address or expand upon Konig's interesting results.

TINNITUS LOUDNESS & PITCH

A distinct and significant frequency dependence of tinnitus pitch likeness match corroborates the earlier work of Norena et al. (2002), although individual data (figure 2A) are widely variable. One possible explanation for this somewhat greater variability is that Norena tested only subjects reporting tonal tinnitus. Our sample included not only tonal forms but cases with broader bandwidth ("ringing" and "hissing" tinnitus). However, we attempted to equate the sounds used for tinnitus pitch matching to the bandwidth of the tinnitus using BPN5 and BPN15 maskers, in order to increase their similarity. This would have been expected to reduce variability in likeness judgments. In our data variability did not appear to depend markedly on tinnitus bandwidth.

Reed's (1960) report of multi-tonal or otherwise non-tonal tinnitus in nearly 75% of subjects is borne out not only by the number of subjects (56.2%) who reported a tinnitus of ringing or hissing quality but also by the lack of distinct peaks in likeness matches, even in the individual data (figure 2) for those subjects who described their tinnitus as tonal. Curiously, a drop in average pitch likeness rating was observed at high frequency (12 kHz in the tonal group, 10-12 kHz in the ringing group). This may be due to some subjects' low similarity ratings for these stimuli because of an inability to perceive them at frequencies with significant threshold shift: maximum stimulus levels may have been, in those cases, near or below threshold. The relatively narrow bandwidth of the stimuli in these groups (BPN5 and pure tones) were also much less likely to be perceived via off-frequency listening than those of the hissing group, which showed no such pronounced high frequency drop.

The broad nature of the tinnitus spectra in all but a few individual cases suggests the implication of a larger cortical area than one at or near an "audiometric edge frequency," and further supports the hypothesis of Eggermont & Roberts (2004) that distributed disinhibition and neural synchrony, rather than remapping of cortical neural frequency tuning to the auiometric edge, gives rise to the tinnitus percept.

RESIDUAL INHIBITION

Results from the frequency-dependence of residual inhibition demonstrate a similar pattern to those of tinnitus pitch. Though most subjects (74%) reported some reduction of their tinnitus, not all subjects did. This observation is consistent with previous reports (Vernon & Meikle 2003). It may be that failure to induce RI in 100% of subjects resulted from too narrow a set of masking stimulus parameters. In fact, RI depth and duration showed the greatest frequency dependence, and the greatest depth, for those subjects who reported a "hissing" tinnitus, for which masking stimuli may have best approximated the tinnitus sensation. The significant effect of masker center frequency on the depth of tinnitus suppression in the overall average suggests that although the stimuli may not have been as effective for tinnitus of a narrower bandwidth, they were effective nonetheless and further manipulations might increase both the proportion of subjects experiencing RI and the depth and duration thereof.

It is noteworthy that low-frequency stimuli (<4 kHz) and white noise increased the loudness of several subjects' tinnitus, but only in the cases where subjects reported a tonal or ringing tinnitus. Several factors may account for increased tinnitus after listening to low frequency masking sounds. Feldmann's (1983) comprehensive study of tinnitus masking established that complete

masking of the tinnitus sensation was required in order to induce residual inhibition. Mitchell's (1983) interpretation of tinnitus masking studies showed that stimulus levels required to completely mask tinnitus sensations were in fact lowest (in terms of sensation level) within the region of auditory threshold shift. Some of the subjects reported herein may not have experienced complete masking at low masker frequencies and this may have been the cause of those cases in which subjects experienced a worsening of the tinnitus sensation. Unfortunately, due to the bandwidth of the sounds, no means of quantifying the sensation level of BPN15 stimuli is possible.Considered in light of previous findings relating minimum masking level (MML) to the induction of residual inhibition, these findings are unsurprising. A standardized MML approach might prove more consistent in producing residual inhibition than the equal-loudness approach used in this experiment.

The even greater variability observed in the duration of RI might also be explained (and avoided in the future) with MML standardization rather than equal-loudness masking stimuli. Though RI did, as expected, increase with duration on the whole, four substantial factors constrained what might otherwise have been a more robust frequency-dependent relationship, and greater overall duration of RI. First, subjects in this experiment were asked first to rate the depth

of RI, and only after completing the ratings did they attend to its duration, which constrained in absolute terms the minimum duration, as each depth rating required at least several seconds. Consequently, duration was measured from the completion of RI depth rating, and did not include the (somewhat variable) time during which subjects were assessing the first parameter. Second, the maximum masking duration was constrained (due to overall duration of the experiment) to 45s, and many subjects reported residual inhibition at or well in excess of this. Third, several subjects reported a residual inhibition induced early in the test procedure which produced a prolonged RI from which tinnitus recovered only partially or did not recover at all (with one subject reporting a day's relief) and were thus unable to report, other than for a few initial masking stimuli, whether some maskers were more effective than others. Finally, previous parametric studies of residual inhibition (Terry et al. 1983, Tyler & Conrad-Armes 1984) showed an effect of masker intensity whereby level above MML influenced the duration of RI, and the equal-loudness approach may have been less than optimal in controlling for this effect.

The high degree of variability mirrors, to some extent, previous attempts to quantify the relation between masking time and RI duration. While Terry et al. (1983) report a logarithmic relation of RI duration to masker length for maskers

between 10s and 10 min, with very few subjects reporting RI less than 10s, Vernon & Meikle (2003) report that some subjects experienced minutes of RI with maskers of one minute's duration.

While the high variability in the duration of subjects' RI was unexpected, the frequency dependence of residual inhibition depth comes as no surprise. According to the neural model proposed by Eggermont & Roberts (2004), the tinnitus percept arises in the absence of intracortical or corticothalamic inhibition driven by external stimuli. The evident pattern of sensorineural hearing loss in our subject cohort shows a standard pattern of high frequency hearing loss, and as Eggermont & Roberts' model predicts, our subjects' tinnitus spectra correspond to the pattern of hearing loss, with high ratings of tinnitus likeness overlapping the region of hearing loss. The observed frequency dependence of residual inhibition follows a similar pattern, in which the greater effectiveness of high frequency masking stimuli may be interpreted as a mechanism whereby peripheral stimulation temporarily re-establishes some inhibition within the region of auditory system corresponding to both hearing loss and the tinnitus percept.

rTMS, COCHLEAR IMPLANTS & THE RI MECHANISM

Interpretation of the psychoacoustic properties of RI is further informed by studies of tinnitus suppression in cochlear implant users and in direct cortical stimulation via rTMS. Osaki et al. (2005) propose that a phenomenon of tinnitus suppression after masking with cochlear implant stimulation is at least analogous, if not identical in mechanism, to residual inhibition in the psychoacoustic reports of cochlear implant users with tinnitus. These tinnitus subjects showed differences between tinnitus present and residual inhibition conditions in PET-imaged regional cerebral blood flow, predominantly in anterior temporal lobe and, curiously, in cerebellum. While the cerebellar locus of activity is puzzling, Osaki et al. interpret the increased temporal lobe activation during RI as an indication of attentional processes in the generation of this phenomenon.

Repetitive transcranial magnetic stimulation (rTMS) in tinnitus sufferers reveals a slightly different and more consistent story. Langguth et al. (2006a) demonstrate not only increased activation of primary auditory cortex (PAC) in tinnitus sufferers, but also a highly left-lateralized bias of this hyperactivity in tinnitus sufferers (regardless of the laterality of the tinnitus itself). This lateralization of the central processors of tinnitus further suggests a central locus of tinnitus generation, because a more peripheral location would likely cause both

auditory cortices to subtend tinnitus. Increased PAC activity would, in such a case, be more likely to be found in either hemisphere, and have its laterality predicted by the location of unilateral tinnitus percepts.

Treatment of the left PAC with low frequency rTMS, which is known to depress activity in hyperexcited neural circuits, yielded a reduction in most subjects' tinnitus severity (Langguth et al. 2006b), and subjects' response to treatment was predicted by the degree of hyperactivity in left PAC, with lower hyperactivity corresponding to better treatment outcome.

Taken into consideration alongside results showing tinnitus suppression increasing with duration (Plewnia et al. 2007) and with intensity (DeRidder et al. 2004) of rTMS treatment, this result is strongly suggestive of a correspondence between psychoacoustic residual inhibition induced by maskers and tinnitus suppression via rTMS. The results herein may, in fact, recommend refined targets for more precise rTMS treatment via neuronavigation to high frequency (ie. anterior) auditory cortical areas.

IMPLICATIONS FOR THE TREATMENT OF TINNITUS

Few, if any, effective treatments for tinnitus are currently available. The use of residual inhibition as a therapeutic approach in tinnitus has been practiced for some time by Vernon and colleagues (Vernon & Meikle 2003) and attempted by others (Watanabe et al. 1997) with mixed success. The results described herein may serve to improve treatment outcomes, as patients' residual inhibition functions and even audiograms might be used to optimize masking stimuli for use in clinical applications. By selecting more suitable maskers to produce residual inhibition (as compared to broadband or white noise used by other experimenters to induce RI) patient outcomes could be improved significantly.

While the duration of RI is, in most cases, only seconds or minutes, Vernon & Meikle (2003) report that some subjects experienced profound psychological relief from even short periods of tinnitus suppression. It should be noted, anecdotally, that a few subjects in this study expressed surprise and gratitude for the relief induced by RI, and one subject remarked that she experienced "the best sleep [she'd] had in years" after testing. Thus, it seems justified to suggest that investigation of the clinical benefit of RI is warranted.

IMPLICATIONS FOR EXPERIMENTATION & REMAINING QUESTIONS

A means of manipulating tinnitus in a completely non-invasive fashion would offer a powerful tool for further research into tinnitus. Residual inhibition, optimized using the techniques described herein, could enable experimental manipulation of the tinnitus percept for further psychoacoustic studies. fMRI brain imaging and EEG, which both require a baseline and comparison condition, are ideally suited as an alternative method to explore further the results of this experiment. Previous results suggest that EEG (Kadner et al. 2002) and MEG (Wienbruch et al., 2006; Muhlnickel et al, 1998) offer some promise in understanding the neural basis of tinnitus, and residual inhibition opens several new avenues of research in this regard.

The frequency dependence of residual inhibition suggests that treatment approaches involving acoustic stimulation should focus on the regions of greatest threshold shift, which in most cases falls in the high- to very high range of human hearing. Devices designed to produce random high frequency filtered noise or to selectively amplify high frequency environmental stimuli above the range of conventional hearing prosthetics offer some promise.

One outstanding question regarding residual inhibition is its relationship with temporary auditory threshold shift (TTS). Though at first the two may seem unrelated, Henry & Meikle (2000) point out that similarity in the time course of both suggest a possible correlation between these phenomena. While this may still be worthy of investigation, accurate measures of TTS are exceedingly difficult to achieve on such a short timescale. Furthermore, it is unclear whether, (even if the two are related) there is any implication of TTS for either the mechanism of tinnitus or its treatment.

Perhaps a more significant question is the role played by areas outside of primary auditory pathways in the etiology of tinnitus and RI. A growing body of evidence (Kadner et al. 2002, Cuny et al. 2004, Petkov et al. 2004) implicates other cortical areas in the attentional modulation of activity in PAC (generally) and in tinnitus. These higher-order functions suggest that tinnitus, as with other auditory percepts, might be modulated by training tinnitus sufferers to improve their performance on auditory discrimination tasks, such as segregation training as demonstrated by Liu et al. (2000) or attention tasks, like those demonstrated by Braun et al (2002).

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