The Role of the Insula Cortex in the Final Common Pathway for Tinnitus: Experience Using Ultra-High-Frequency Therapy

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Abstract: The insula cortex (Brodmann's 13–16) has distinct auditory and multisensory areas that have been identified through imaging to be active or hypoactive in cases of severe tinnitus. As such, the insula is a candidate for inclusion in the final common pathway (FCP) for tinnitus. The insula has connection with the prefrontal and auditory cortices, amygdala, thalamus, parabrachial nucleus, orbitofrontal cortex, striate, cuneus, and cerebellum. The insula, as part of the medial temporal lobe system—which also includes the amygdala and the hippocampus—modulates its metabolic activity after high-frequency stimulation. The FCP is characterized by numerous areas in the lemniscal and extralemniscal pathways, including the auditory regions in the thalamus, the cortex, and the cerebellum. It is suggested that elements of the FCP, formulated into a general model of tinnitus, should be considered as beads on a string in designing treatment strategies. This view is the direct result of our past and recent new experiences using ultra-high-frequency sound therapy in cases of severe disabling tinnitus, presented at this time. Behaviorally, tinnitus symptoms decrease by self-report and changes in minimal masking levels with high-frequency sound therapy. The use of multisensory vibration stimulation (somatosensory and high-frequency jointly) should also be explored to maintain or reprogram the auditory cortical map and induce activity in the FCP circuit, including the parabrachial nucleus and the insula, which may be the physiological substrate of tinnitus behavioral tests.

Key Words: insula; high-frequency sound therapy; tinnitus

Tinnitus, a perception that seemingly appears to be a ringing in the ears to many, actually involves numerous spatially and temporally distributed neural circuits with summed outputs that have been collectively termed the *final common pathway* (FCP) in severe disabling tinnitus. This FCP is characterized by activity at the neuronal and molecular levels in the lemniscal and extralemniscal pathways, including the auditory regions in the thalamus, cortex, medial temporal lobe (MTL; limbic) system, cerebellum, and other cortical areas [1–7]. The auditory nature of the limbic system and the cerebellum was proposed decades ago and is now completely accepted [1–3].

The MTL system, including the amygdala and the hippocampus (involved in processing emotions and memory), is connected into the lemniscal and extralemniscal pathways at both the cortical and subcortical levels. It is hypothesized that the initial process in the transformation of a sensory stimulus to one of affect is the establishment of the aberrant auditory memory in tinnitus [1]. Reciprocal neuronal connections among the MTL system—orbitofrontal cortex, prefrontal cortex, striate, cuneus, and hypothalamus—modulated by the insula transform the sensory component of the aberrant auditory stimulus into one of affect. This process establishes the paradoxical auditory memory and psychomotor and autonomic responses, manifested clinically in the behavior of the

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tinnitus patient [5,6]. Evidence is reported here that the insula cortex is active in both tinnitus and its treatment.

METHODS

Subjects

The subjects of this study were six adults with severe disabling tinnitus (four male, two female; age range, 35–72 years). All subjects were evaluated for tinnitus, including audiograms and pitch matches, as part of a comprehensive medical-audiological tinnitus patient protocol (MATPP) [8], as well as outcomes questionnaires [9]. All had mild to moderate high-frequency hearing loss, and their tinnitus pitch was high, matching either a pure-tone or narrow-band noise at between 5 and 16 kHz (averaging some 7.5 kHz).

Stimulus

The tinnitus treatment stimulus was produced with a sound synthesizer using Kyma Version 5 software with a Capybara 320 Sound Computation (Symbolic Sound Corporation, Champaign IL, USA) and was recorded on a compact disk. The stimulus was digitally processed, filtered music modulated at a 16-kHz tone (phase-suppressed) with a spectrum ranging from 6 to 20 kHz. The compact disk signal was fed through a custom-made amplifier into a piezoelectric bone conduction transducer. The transducer was held in place on the right mastoid bone of the subject by a headband. Though the stimulus was presented to the right ear, it was heard binaurally [10].

The transducer is a custom-made aluminum ceramic composite with an upper-frequency limit of approximately 50 kHz. The lowest response is near 6 kHz (lowest resonant peak), which allows standard calibration when mass-loaded with the head or an artificial mastoid. This commercially available tinnitus treatment system, the UltraQuiet* system (Sound Technique Systems, LLC, Richmond VA, USA), has a maximum output of 53 dB HL (hearing level) when it is mass-loaded with 5.4 Newtons of force [11]. The transducer, headband, and amplifier were all approved by the U.S. Food and Drug Administration prior to use in this study. This study had local and Western institutional review board approval.

Procedure

The subjects listened to the tinnitus treatment stimulus for fourteen sessions (twice per week for 8 weeks), beginning with one-half session in week 1 only (30 minutes). The remaining sessions were 60 minutes in duration. The stimulus was presented at 12 dB SL (12 dB above sensation level or threshold).

The study was a before-and-after single-subject repeated-measure design. Audiological evaluation included pure-tone audiometry, speech audiometry, tinnitus pitch and loudness matching, and masking curves to establish minimal masking levels (MMLs) at 250–8,000 Hz using both narrow-band and white noise. Classification of masking curve type according to the Feldmann's system was applied [12]. Outcome questionnaires for establishing a baseline were administered prior to the first session and after the final session (a long-term follow-up questionnaire 8 weeks after the final session) [9]. Data presented here were collected as part of a larger study [2] and are reported here for the first time.

Positron emission tomography (PET) was initially performed within 1 week prior to the start of sound therapy to establish a baseline and at the conclusion of 8 weeks of therapy (5 minutes to within a few hours). PET scans were performed at the Radiation Physics Department of the University Hospital of Brooklyn. After intravenous administration of 8.0 mCl of F^{18}- fluorodeoxyglucose, scanning was performed. PET results were obtained before and after the UltraQuiet sessions, and images were read in a blinded fashion by the same board-certified neuroradiologist. The percent of metabolic change in the insula of the MTL, the final physiological state (hyper- or hypometabolic), the direction of metabolic change (hypermetabolic to hypometabolic) after 8 weeks of high-frequency therapy, and laterality of metabolic activity were obtained. The percent of metabolic change was a simple comparison of the before and after standard uptake values (SUV), previously described elsewhere in detail [2] as:

$$\text{SUV} = \frac{\text{Tracer uptake}}{\text{Administered dose/Patient weight}}$$

In this metric, the subject's pretest value serves as the control for the posttest value.

The final physiological state for each subject was classified as either hypometabolic or hypermetabolic. The direction of metabolic change was the movement after therapy to either a hypometabolic or hypermetabolic state. For subjects with bilateral tinnitus, the relative strength of the metabolic activity right (R) versus left (L) was determined.

The change in the MMLs and the assessment of tinnitus relief by questionnaire [2,9,13] took place after the

* UltraQuiet™ is a proprietary tinnitus treatment developed by Sound Technique Systems, LLC, with a US patent issued and others pending. Martin Lenhardt holds an equity position in Sound Technique Systems and serves as Vice President of Research and Technology. He was not directly involved in the data collection. The UltraQuiet device is FDA approved.

Subject	%c	Final	Direction with Therapy	Lateral	MMLc −dB HL	Improvement 8 wks Posttherapy*
1	−1	hyper	↑	L < R	7	5
2	−29	hypo	↑		12	6
3	−18	hypo	↓		9	4
4	+44	hypo	↓		46	6
5	+17	hyper	↓	L < R	46	6
6	−16	hyper	↑	L < R	6	5

*4 = no change; 5 = fair; 6 = good; 7 = very good.
↑ hypo to hyper; ↓ hyper to hypo.

Figure 1. Insula and high-frequency bone conduction therapy: summary of data from six patients with severe tinnitus, exhibiting changes in the insula cortex and related behavioral indices. Depicted are subjects, percent change in the insula metabolism from pre- to post-testing (*%c*), the final metabolic condition of the insula after therapy (*final*), the direction of metabolic change with therapy (*direction*), the laterality difference between the right and left insulas (*lateral*), the change (reduction in decibels) in the minimal masking levels after therapy (*MMLc*), and the improvement in tinnitus relief 8 weeks after therapy.

last therapy session and prior to the second PET scanning. The classification of tinnitus symptom decrease is presented on a 4-point scale in which 4 = no change; 5 = fair improvement; 6 = good improvement; and 7 = very good improvement by subject report.

RESULTS

Comparing the final scan with the initial scan in a small number of patients does not allow more than stating that some effect occurred in all the subjects. The final state was hypermetabolic in one-half the subjects (three) and hypometabolic in the other three subjects. However, if the change in MMLs after therapy are considered (Fig. 1), it is suggested that a change from hypermetabolism to hypometabolism is associated with the best clinical outcome by subject report of tinnitus relief. Five of six subjects experienced tinnitus relief owing to the high-frequency therapy, whereas one subject reported no change. All subjects did exhibit a considerable reduction in the needed masking energy to cancel tinnitus symptoms. No subject experienced a worsening of tinnitus.

The success rate was 83% in this small sample of patients. Nonetheless, these patients had reported no benefit from instrumentation tinnitus therapies or medication, suggesting the utility of the present technique in treating severe disabling tinnitus. It must be recognized that changes are occurring in other regions of interest beyond the insula [2]; thus, activity at one site may be only a possible contributor to the global brain change and behavioral result. The persistent sense that tinnitus is still annoying even after considerable reduction in minimal masking levels might be attributable to the role of the insula in tinnitus.

Tinnitus results in a complex pattern of distributed activity: The insula, along with the auditory cortex and the cerebellum, is part of that pattern. The insula has connections via the parabrachial nucleus and sensory pathways to both the auditory and somatosensory periphery. The FCP appears to be activated very early on after an "exposure" to noise or an ototoxic drug. There is strong evidence that both auditory and nonauditory structures are active after one high-intensity exposure [14]. The FCP is extensive and interactive on the subcortical and cortical levels [1–3]. Temporal and temporofrontal cerebral regions are active in the FCP, as reflected in changes in the standard frequency bands in quantitative electroencephalography [15] and in the high-frequency (>40–80 gamma) range over the auditory cortex [16]. These data support the anatomical sites of the FCP concept and its physiological basis in those variations in electrophysiology with severe tinnitus, as postulated in flux in the synchrony and dyssynchrony among sites [15–17]. The flux is a dynamic feature of the interaction of neural responses from multiple sites. There are alterations in the excitatory and inhibitory responses that result in a form of neural subtraction that culminates in the tinnitus percept. The dyssynchrony can initially occur in the peripheral auditory system but can quickly cascade into multiple central sites in the FCP. The focus on the central pathways should not suggest that molecular processes, *N*-methyl-D-aspartate and γ-aminobutyric acid are not important in tinnitus [18–20]. However, the application of high-frequency sound to reduce tinnitus [21] has great clinical applicability [9,13].

The inclusion of the insula, with its multisensory sensitivity in the FCP, raises the possibility that somatosensory stimulation might also be an effective treatment tool [22]. Postauricular muscle vibration is one such treatment that induces inhibition in the dorsal cochlear nucleus through somatosensory system inhibition and can potentially alter bodily feeling via the parabrachial and the insula [5,23]. Combining this with high-frequency stimulation should result in multiple synergistic effects: inhibition of the dorsal cochlear nucleus, reduction in spontaneous neural firing rates, stimulation of multisensory neurons, and prevention of cortical map reorganization, summing to reduce perceived tinnitus severity.

The insula's newly discovered role in maintenance of addictions—in particular smoking [24,25]—is also encouraging in that high-frequency sound stimulation alters the physiology after tinnitus treatment. This concept is consistent with our best tinnitus outcomes associated with an insula change from *hyper*active to *hypo*active. Considering tinnitus an addiction is not far-fetched: There is evidence that listening to loud music has many of the

characteristics of addiction [26]. Tinnitus can be considered perceptually salient internal sound. Perhaps the insula contributes to the overall pattern of tinnitus relief and stress reduction in the presence of persistent sound annoyance, as we had observed with high-frequency stimulation therapy [9,13].

CONCLUSION

The insula cortex (Brodmann's 13–16) has distinct auditory and multisensory areas that have been identified through imaging to be active or hypoactive in cases of severe tinnitus. That is to say, the insula is active in tinnitus and with tinnitus treatment using high-frequency sound therapy. Owing to its tinnitus activity, the insula is a candidate for inclusion in the FCP. The FCP for tinnitus includes the lemniscal and extralemniscal pathways to the auditory cortices and the insula. The FCP receives contributions from the frontal and parietal regions and from the cerebellum and MTL system. The MTL system, including the insula, can activate the parabrachial nucleus that, in turn, can produce the somatic, emotional, uneasy sense or "bad" feeling often associated with severe tinnitus. The insula should be considered an active site in the MTL system, which can be physiologically modified with sound therapy. Its role in maintaining tinnitus has yet to be completely determined.

REFERENCES

1. Shulman A. A final common pathway for tinnitus—the medial temporal lobe system. *Intl Tinnitus J* 1:115–126, 1995.
2. Shulman A, Strashun AM, Avitable J, et al. Ultra-high frequency acoustic stimulation and tinnitus control: A positron emission tomography study. *Int Tinnitus J* 10(2):113–125, 2004.
3. Shulman A, Strashun A. Descending auditory system/cerebellum/tinnitus. *Int Tinnitus J* 5(2):92–106, 1999.
4. Shulman A. Tinnitus neural substrates: An addendum. *Int Tinnitus J* 11(1):1–3, 2005.
5. Lenhardt M, Shulman A, Goldstein B. The role of the parabrachial nucleus in the natural history of tinnitus and its implications. *Int Tinnitus J* 13(2):87–98, 2007.
6. Shulman A. Final common pathway for tinnitus—update: 2008. Anatomic substrates. Presented at the Thirty-fifth International Neuroequilibriometric Society Congress, Bad Kissingen, Germany, April 10–13, 2008.
7. LeDoux JE, Cicchetti P, Zagoraria A, Romanski LM. The lateral amygdaloid nucleus: Sensory interface of the amygdala in fear conditioning, *J Neurosci* 10:1062–1069, 1990.
8. Shulman A. Medical-audiologic tinnitus patient protocol. In *Tinnitus Diagnosis and Treatment*. Philadelphia: Lea & Febiger, 1991:319–321.
9. Goldstein B, Shulman A, Lenhardt ML, et al. Long-term inhibition of tinnitus by UltraQuiet therapy: Preliminary report. *Int Tinnitus J* 7(2):122–127, 2001.
10. Lenhardt ML, Richards DG, Madsen AG, et al. Measurement of bone conduction levels for high frequencies. *Int Tinnitus J* 8(1):9–12, 2002.
11. Cai Z, Richards DG, Lenhardt ML, Madsen AG. Response of human skull to bone conducted sound in the audiometric to ultrasonic range. *Int Tinnitus J* 8(1):1–8, 2002.
12. Feldmann H. Homolateral and contralateral masking of tinnitus by noise bands and pure tones. *Audiology* 10:138–144, 1971.
13. Goldstein BA, Lenhardt M, Shulman A. Tinnitus improvement with ultra high frequency vibration therapy. *Int Tinnitus J* (11)1:14–22, 2005.
14. Zhang JS, Kaltenbach JA, Wang J, Kim SA. *Fos*-like immunoreactivity in auditory and nonauditory brain structures of hamsters previously exposed to intense sound. *Exp Brain Res* 153:655–660, 2003.
15. Shulman A, Avitable MJ, Goldstein B. Quantitative electroencephalography power analysis in subjective idiopathic tinnitus patients: A clinical paradigm shift in the understanding of tinnitus, an electrophysiological correlate. *Int Tinnitus J* 12(2):121–131, 2006.
16. Ashton H, Reid K, Marsh R, et al. High-frequency localized "hot spots" in temporal lobes of patients with intractable tinnitus: A quantitative electroencephalographic (QEEG) study. *Neurosci Lett* 426(1):23–28, 2007.
17. Shulman A, Goldstein B. Tinnitus dyssynchrony-synchrony theory: A translational concept for diagnosis and treatment. *Int Tinnitus J* 12(2):101–114, 2006.
18. Guitton, MJ, Dudai Y. Blockade of cochlear NMDA receptors prevents long-term tinnitus during a brief consolidation window after acoustic trauma. *Neural Plasticity* 2007(1):80904, 2007.
19. Guitton MJ, Puel J-L. Cochlear NMDA receptors and tinnitus. *Audiol Med* 2(1):3–7, 2004.
20. Brozoski TJ, Spires TJ, Bauer CA. Vigabatrin, a GABA transaminase inhibitor, reversibly eliminates tinnitus in an animal model. *J Assoc Res Otolaryngol* 8(1):105–118, 2007.
21. Noreña AJ, Eggermont JJ. Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. *Neuroreport* 17(6):559–563, 2006.
22. Lenhardt ML, Goldstein BA, Shulman A, Guinta R. Use of high frequency and muscle vibration in the treatment of tinnitus. *Int Tinnitus J* 9(1):32–36, 2003.
23. Craig AD. How do you feel? Interoception: The sense of the physiological condition of the body. *Nat Rev Neurosci* 3:655–666, 2002.
24. Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. *Science* 26(315):531–534, 2007.
25. Franklin TR, Wang Z, Wang J, et al. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: A perfusion fMRI study. Neuropsychopharmacology 32 (11):2301–2309, 2007.
26. Florentine M, Hunter W, Robinson M, et al. On the behavioral characteristics of loud-music listening. *Ear Hear* 19 (6):420–428, 1998.