Ultra-High-Frequency Acoustic Stimulation and Tinnitus Control: A Positron Emission Tomography Study

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Abstract: Ultra-high-frequency (UHF) external acoustic stimulation with the UltraQuiet device (UQ) has been reported to provide significant relief of severe disabling-type tinnitus. The nuclear medicine imaging technique of positron emission tomography (PET) was selected as a monitoring system to compare objectively metabolic alterations in brain function before and after UHF/UQ and to correlate the PET data with the subjective behavioral response of patients reporting tinnitus relief. PET of brain was completed on 6 patients randomly selected from a cohort of 15 patients included in a protocol to establish long-term tinnitus relief with UHF/UQ. Twelve specific regions of interest (ROI) were selected for PET of brain examination on the basis of results obtained with single-photon emission computed tomography (SPECT) of brain examinations recommended for patients with severe disabling-type tinnitus and demonstrating significant perfusion asymmetries in the right and left brain ROI of the primary auditory cortex; frontal, temporal, parietal, and medial temporal lobes; and cerebellum. PET of brain results included ratios of post- and pre-UHF/UQ stimulation that demonstrated no random response in the selected PET of brain ROI and ratios of post- and pre-UHF/UQ stimulation that demonstrated three categories of response in the selected PET brain ROI for all six patients: hypermetabolism in three patients; hypometabolism in two; and a mixed response in one. Correlation was established for each patient among PET and electrophysiological responses of alteration in minimal masking levels, the residual UHF neuronal response as reflected in the UHF audiogram, and the subjective reported behavioral responses of patients (obtained from outcome questionnaires for tinnitus relief, which focused on tinnitus intensity, annoyance, severity index, and a subjective scale of value of the UHF/UQ device for tinnitus relief. The subjective behavioral response for tinnitus relief with UHF/UQ was found to reflect a dual effect: acoustic stimulation of the residual neuronal function in the UHF range (10–14 kHz) and audiometric thresholds of 40–50 dB sound pressure level (SPL), and the metabolic activity at brain cortex for neuronal reprogramming. The PET of brain categories of response suggested that the UHF/UQ "masking" is predominantly reflective of neuronal reprogramming at the brain cortex. Nuclear medicine PET of brain imaging has provided an objective monitoring system for attempting to establish the efficacy of UHF/UQ for tinnitus relief. No complication of the tinnitus was reported secondary to the PET of brain examination. This limited PET of brain study supports the clinical recommendation of the efficacy of UHF/UQ external acoustic stimulation for a selected population of patients with tinnitus of the severe disabling type.

Key Words: minimal masking levels; positron emission tomography; single-photon emission tomography; tinnitology; ultra-high-frequency

ince 1989, nuclear medicine imaging has been introduced into the discipline of tinnitology for both basic science and clinical diagnosis and treatment. For basic science, nuclear medicine imaging attempts to understand and identify underlying mechanisms of tinnitus production and translational neuroscience for establishing structure and functional relationships of brain and ear and to identify its underlying molecular genetic neurochemistry [1–4]. Clinically, nuclear medicine imaging attempts to correlate structure and function, to identify conditions associated with tinnitus, to improve the accuracy of the diagnosis of the tinnitus symptom, and to monitor the efficacy of therapeutic modalities focused on tinnitus relief [5,6].

Ultra-high-frequency (UHF) external acoustic stimulation with the UltraQuiet (UQ) device (UHF/UQ) for attempting tinnitus relief has demonstrated significant initial success in providing short- and long-term tinnitus relief [7–13]. The nuclear medicine imaging technique of positron emission tomography (PET) was included in a study protocol for 6 patients randomly selected from a cohort of 15 patients with tinnitus of the severe disabling type (SIT). Attempts were made to establish the efficacy of UHF for tinnitus relief both short-term (1 week) and long-term (8 weeks).

PET of brain, a direct indicator of glucose metabolism, a metabolic correlate of cerebral neuronal function and its relationship to structure, was selected to establish objectively a measure of comparison of the efficacy of UHF/UQ for short- and long-term tinnitus relief [14,15]. Furthermore, it was employed to monitor what, if any, alteration in brain metabolism occurred in brain regions of interest (ROI) selected for data analysis and to correlate the PET data with parameters of subjective hearing, balance, behavior, and electrophysiological responses of the cochlear vestibular system, both peripheral and central. Selection of the ROI for PET of brain analysis was based on a clinical experience with single-photon emission computed tomography (SPECT) of brain, ongoing since 1989 at Downstate Medical Center–State University of New York. This clinical experience has revealed perfusion asymmetries in multiple regions of brain, highlighted by the frontal, temporal, medial-temporal, and parietal lobes and the cerebellum (A.M. Strashun, personal communication) [1–5]. This study reports the PET of brain results of 6 patients (of a cohort of 15) who were treated with UHF/UQ for 1 and 8 weeks and discusses its basic science and clinical implications.

MATERIALS AND METHODS

Six patients with SIT were randomly selected for brain PET of brain imaging from a cohort of 15 SIT patients in whom the effects of external acoustic stimulation with UHF/UQ, both short-term (1 week) and long-term (8 weeks), were being studied for tinnitus relief. All 15 patients had completed the medical-audiological tinnitus patient protocol and the outcomes questionnaires [11,12,16,17]. The short- and long-term results of this study of the 15 tinnitus patients stimulated with UHF/UQ for tinnitus relief have been reported [11–15].

PET of brain was performed initially within 1 week before UHF/UQ to establish baseline data and at the conclusion of 8 weeks of therapy. The final PET of brain imaging was completed within 5 minutes of the last UHF therapy (n = 5) and within 12 hours (n = 1).

PET of Brain Technique

PET of brain was obtained with a Siemens Exact 47 ECAT scanner (Siemens/CTI). All acquisitions were performed in a two-dimensional mode. All emission data were attenuation-corrected using standard 68-germanium transmission algorithms. All patients were scanned at 1 hour after intravenous administration of a standard 10-mCi dose of fluorine-18-2-deoxyfluoroglucose (^{18}F-FDG).

Data were transferred to a SUN workstation (SUN Microsystems, Inc.) and analyzed using commercially available Siemens/CTI software. Anatomical tissue images were generated, and standard circular ROI were created for each patient in the study. The 12 areas studied included the left and right thalamus; the temporal, auditory, parietal, and frontal lobes; and the cerebellum (A.M. Strashun, personal communication).

Standard uptake values (SUV) were calculated for each ROI using the following formula:

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

Paired *t*-tests were used to investigate differences for both interhemispheric and intrahemispheric differences in the 12 ROI. SUVs were normalized by dividing the ROI by the value of the total brain. Data for each patient were paired, using each patient as his or her own control to eliminate baseline differences. For each ROI, interhemispheric counts were subjected to analysis for both pre- and post-UHF stimulation. This yielded 12 paired *t*-tests for each calculation. Data were analyzed for both raw and normalized SUVs. The Bonferonni test for multiple comparisons was used to correct for the number of tests performed, and any test that

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* Corrected for lean mass, serum glucose level, camera calibration factors, and time between dose administration and data acquisition.

Table 1. Ultra-High-Frequency Air Conduction Audiograms

Patient ID No.	PET Category	Ear	Frequency				
			10 k	11 k	12 k	13 k	14 k
1	Hyper	Right	80	85	85	95	90
		Left	65	75	75	85	95
2	Hyper	Right	80	90	95	95	90
		Left	75	85	95	95	110
3	Hyper	Right	95	100	115	120	NR
		Left	105	115	NR	NR	NR
4	Hypo	Right	45	65	75	75	80
		Left	35	60	79	80	75
5	Hypo	Right	35	25	25	40	35
		Left	25	20	25	30	35
6	Mixed	Right	35	30	40	60	80
		Left	45	55	70	70	75

Note: Correlation with positron emission tomography of brain metabolic categories.
Hyper = hypermetabolic; hypo = hypometabolic; mixed = mixed metabolic; NR = no response, 120 dB SPL; PET = positron emission tomography.

Figure 1. Ultra-high-frequency air conduction audiograms (right ear) and correlated with positron emission tomography (*PET*) of brain metabolic categories: hypermetabolic (*hyper*), hypometabolic (*hypo*), and mixed metabolic (*mixed*).

produced a significance level of less than .00416 was considered significant at the .05 level. The same analysis was performed on the intrahemispheric recordings, comparing each ROI before and after UHF stimulation.
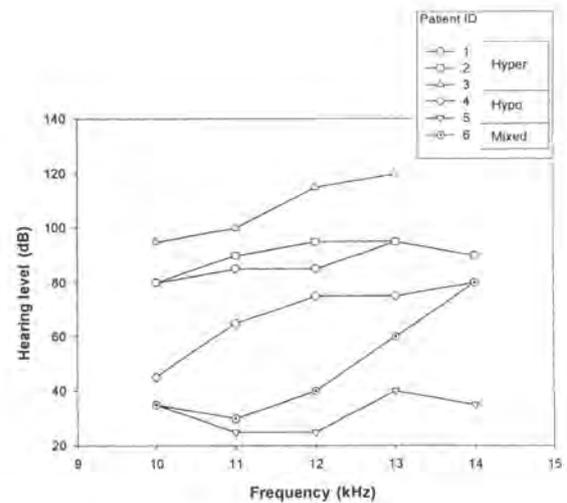
Audiology

Attempts were made to establish audiological correlates between the PET of brain metabolic findings and (1) UHF auditory thresholds at 10–20 kHz (Table 1); (2) minimal masking levels (MMLs; Table 2; Figs. 1, 2); and (3) classic conventional audiometric thresholds (i.e., 250 Hz–8 kHz) [12–15]. Six patients with SIT were randomly selected from a cohort of 15 such patients for study of the effects of external acoustic stimulation with UHF/UQ and their efficacy for tinnitus relief. Patients were randomly assigned to one of three

groups. Group 1 patients received stimulation twice weekly for 2 weeks, were deprived of stimulation for 2 weeks, and then received stimulation twice weekly for 3 weeks for a total of 10 sessions. Group 2 patients received stimulation twice weekly for 3 weeks, were deprived of stimulation for 2 weeks, and then received stimulation twice weekly for 3 weeks, for a total of 12 sessions. Group 3 patients received stimulation twice weekly for 4 weeks, were deprived of stimulation for 1 week, and then received stimulation twice weekly

Table 2. Summary for Each Patient

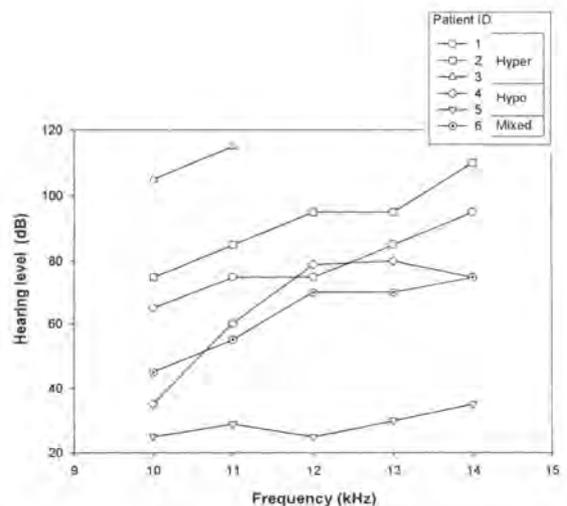| Patient ID	PET Category	MML Change in dB	Subjective Scale		Feldmann Masking Curve (1–4)
			1 Wk After	8 Wk After	
1	Hyper	5–10	5	5	1
2	Hyper	5–20	4	6	1
3	Hyper	5–15	5	4	4
4	Hypo	5–45	4	6	4
5	Hypo	10–35	7	6	4
6	Mixed	5–10	5	5	4

Note: Subjective scale (efficacy of UHF/UQ): 7 = very good; 6 = good; 5 = fair; 4 = no change; 0–3 = poor.
Hyper = hypermetabolic; hypo = hypometabolic; mixed = mixed metabolic; MML = minimum masking level.

Figure 2. Ultra-high-frequency air conduction audiograms (left ear) and correlated with positron emission tomography (*PET*) of brain metabolic categories: hypermetabolic (*hyper*), hypometabolic (*hypo*), and mixed metabolic (*mixed*).

for 3 weeks for a total of 14 sessions. Follow-up was conducted for 1 week (short-term) and 8 weeks (long-term) after therapy had ceased. Correlation was attempted among the groups who received UHF/UQ and the metabolic categories of brain PET for the six tinnitus patients selected for PET of brain imaging.

Behavioral Responses

Behavioral responses to the presence of tinnitus were recorded and evaluated after the SIT patients had completed questionnaires regarding tinnitus intensity, severity, and annoyance [11,12,14,15]. In addition, each patient was asked to respond to several questions.

Tinnitus Severity Index

We attempted to identify subjective tinnitus severity by use of the tinnitus severity index (TSI), which consists of five questions. The test is easily administered, is brief, has clearly defined categories, and is simple for patients to answer. Patients were instructed to mark the degree of interference caused by the tinnitus for sleep, concentration, work performance, communication, and understanding. A rating scale of 0–7 points was used, in which 0 represents no interference and 7 signifies extreme interference. The maximum TSI score is 35.

Scoring was simple. The number marked for each question is viewed individually and then scored for all five answers. A score of 5–7 on any single question indicates extreme severity for that category. A score of 3–4 on any question indicates a grade of moderate severity. A score of 1–2 on any question indicates a grade of mild severity, whereas 0 indicates no interference for a given question category.
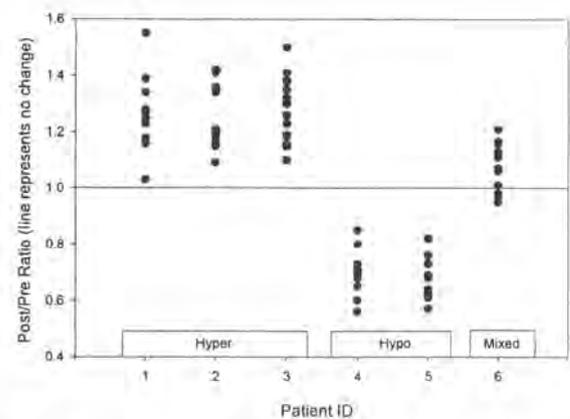
Subjective Evaluation of UHF/UQ Efficacy

Each tinnitus patient's subjective evaluation of UHF/UQ efficacy was rated on a scale of 0–7; very good, 7; good, 6; fair, 5; no change, 4; poor, 0–3. The results were correlated with the PET categories of response (see Table 2).

RESULTS
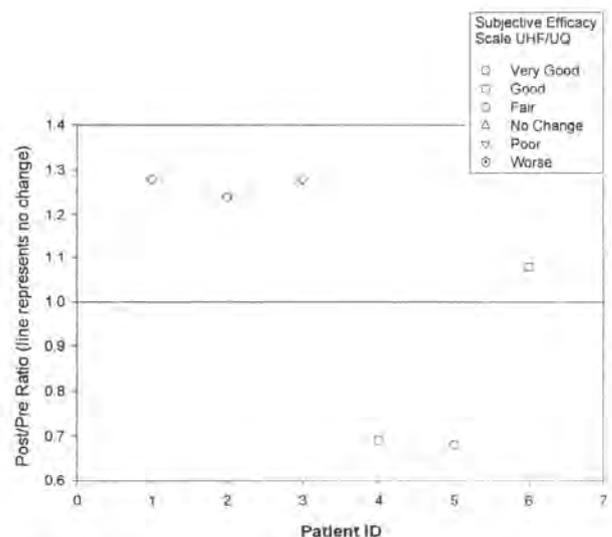
PET of Brain Data Statistical Analysis

Preliminary results indicated that patients who reported the best results had a decrease in activation in all ROI and in the total brain counts, as identified by the ratio of post- and pre-UHF/UQ acoustic stimulation (Figs. 3, 4).

When corrected for number of tests (Bonferroni correction for 12 paired t-tests), the normalized data for the interhemispheric difference in the cerebellum, left
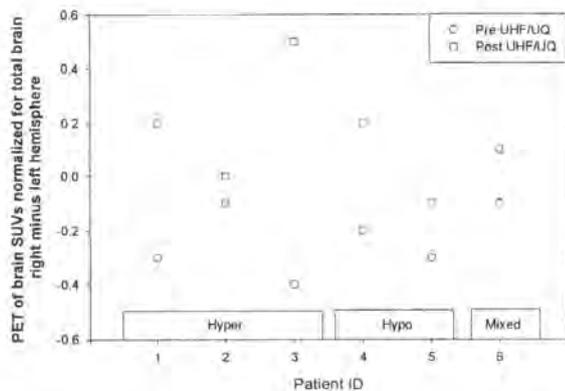

Figure 3. Ratio of before and after positron emission tomography (*PET*) metabolic standard uptake values in selected regions of interest (right and left frontal, right and left temporal, right and left parietal, right and left auditory, right and left thalamus, right and left cerebellum). PET of brain metabolic categories: hypermetabolic (*hyper*), hypometabolic (*hypo*), and mixed metabolic (*mixed*).

versus right, were significant ($p = .003$) before UHF stimulation but were not significant after stimulation. For all patients, the left cerebellum prior to UHF stimulation showed more activity in the left side than the right. After UHF stimulation, only one patient still showed greater activity in the left cerebellum, one showed no difference, and three now showed greater activity in the right cerebellum versus the left side. The t-test for the raw interhemispheric SUVs for the cere-

Figure 4. Ratios of before and after positron emission tomography standard uptake values for the total brain correlated with subjective efficacy scale for ultra-high-frequency Ultraquiet (*UHF/UQ*) treatment.

Figure 5. Cerebellum plots of positron emission tomography (*PET*) metabolic categories before and after ultra-high-frequency Ultraquiet (*UHF/UQ*) stimulation normalized to total brain standard uptake values (*SUVs*). PET of brain metabolic categories: hypermetabolic (*hyper*), hypometabolic (*hypo*), and mixed metabolic (*mixed*).

bellum did not obtain a critical value to be considered significant when corrected for multiple *t*-tests ($p = .0052$; Fig. 5)

We found in all other ROI no significant difference in left versus right hemisphere in either pre- or post-stimulation ($p > .05$). Intrahemispheric recordings showed no significant difference in pre- versus poststimulation ($p > .05$) uncorrected for Bonferroni.

Scattergrams of the raw SUVs for individual patients showed that patients responded individually and differently to UHF stimulation. When they were tested as a group with the paired *t*-test, the difference in responses cancelled out and were not significant.

Plots of the ratio of SUVs in PET of brain ROI of individual post- and pre-UHF stimulation demonstrated three categories of cortical responses in the ROI of brain selected for examination for the six patients: decreased metabolic activity (hypometabolism, n = 2); increased metabolic activity (hypermetabolism, n = 3); and mixed metabolic activity (n = 1; see Fig. 3).

Plots of the ratio of post- and pre-UHF stimulation showed a correlation of PET of brain activation counts with a patient's report of relief from tinnitus with UHF stimulation (see Fig. 4) and with the UHF prestimulus audiogram (see Figs. 1, 2; see Table 1). Three patients (identified as patients 1, 2, and 3) had "fair" relief from symptoms and showed increased activation; one patient (patient 6) reported "good" relief and had a mixed activation pattern; and two patients (patients 4 and 5) reported a very good response to UHF stimulation and showed a decrease in PET SUV counts (see Fig. 4).

Because our sample size was small for this pilot study (six patients), we were not able to factor out the

differences in SUVs on the basis of the patients' level of relief from symptoms. Positive associations were established among the PET of brain metabolic categories of response, UHF audiograms, minimal masking levels, and subjective reports of UHF efficacy for tinnitus relief (see Table 2). No association of response was established between PET of brain metabolic categories of response and the conventional, classic audiogram and tinnitus annoyance [11–15].

The reader is referred to the tinnitus relief results reported both short- and long-term for the behavioral correlates established for UHF/UQ stimulation in the total cohort of 15 patients [12,15].

Audiology

No patient subjectively reported an increase or decrease in hearing loss or tinnitus or vertigo at the conclusion of 1 and 8 weeks of UHF/UQ stimulation and after the brain PET procedures. Classic acoustic stimulation audiograms measuring 250 Hz–8 kHz revealed individual variations in hearing thresholds similar to those reported for the total cohort of 15 patients in the UHF/UQ study [11–15]. All patients reported varying degrees of tinnitus relief (see Table 2).

Correlation of the UHF audiograms and the subjective response of the efficacy of the UHF/UQ with the brain PET metabolic categories revealed a consistent audiometric pattern (i.e., SIT patients with auditory thresholds of 40–50 dB or less for the frequency range of 10–14 kHz subjectively reported the best results for tinnitus relief). The variation in subjective tinnitus relief response (i.e., UHF efficacy for tinnitus relief) correlated with and reflected the auditory threshold and residual neuronal response in the 10- to 14-kHz range (see Figs. 1, 2, 4).

No correlation was established among a PET of brain metabolic category, the Feldmann masking curve, and the subjective scale of the efficacy of UHF/UQ with any PET of brain metabolic category in any tinnitus patient. Two patients reported no significant change in their tinnitus 1 week after stimulation but good relief 8 weeks after. All six patients reported some degree of tinnitus relief either at 1 week or 8 weeks after stimulation. The two patients who reported no significant change in their tinnitus 1 week after stimulation reported a fair degree of relief at 8 weeks after stimulation. No patient reported tinnitus as worse either at 1 or 8 weeks after stimulation (see Table 2).
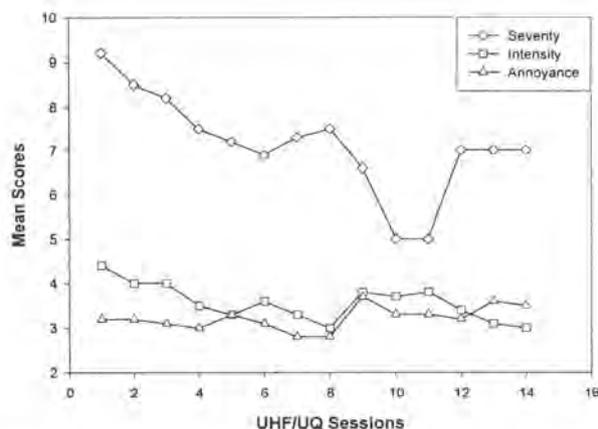
MMLs showed significant reduction at some frequencies for all six patients (see Table 2). The greatest shifts in MMLs were seen in the two patients in the hypoactive PET category, with the maximal shift indicating a 45-dB reduction.

Behavior Outcomes

The best subjective response for efficacy of tinnitus relief with the UHF/UQ device was reported as "very good" by two tinnitus patients. The outcome correlated with the PET of brain metabolic category of hypoactivity and UHF audiometric thresholds of at least 40–50 dB SPL and in the frequency range of 10–14 kHz (see Table 2). The subjective responses reported as "fair" at the conclusion of 1 and 8 weeks of stimulation by three tinnitus patients correlated with PET of brain metabolic categories of hyperactivity and audiometric thresholds greater than 40–50 dB SPL in the frequency range of 10–14 kHz (see Table 2).

The mean TSI data scores for tinnitus severity across UHF/UQ sessions for the six tinnitus patients who completed the PET of brain were altered from 8.5 to 5.6. That result was statistically significant. All six PET tinnitus patients reported a degree of tinnitus relief either at 1 week or 8 weeks after stimulation. Two of the six reported no significant change at 1 week after stimulation but moderate relief at 8 weeks after. In other words, a latency in the subjective report of tinnitus relief was identified in these two patients at the end of 8 weeks of UHF external acoustic stimulation (see Table 2; Fig. 6) [10,11].

Correlation of the group UHF/UQ stimulation results and PET of brain metabolic categories for the six patients revealed hypometabolic activity in group 3 (n = 2); hypermetabolic activity in group 3 (n = 1), group 2 (n = 1), and group 1 (n = 1); and mixed activity in group 3 (n = 1). Apparently, no relationship was established among the group UHF/UQ stimulation results, the PET of brain metabolic category, and the reported tinnitus relief. None of the six SIT patient who com-

Figure 6. Parameter tinnitus identification: mean scores for severity, intensity, and annoyance per ultra-high-frequency Ultraquiet (*UHF/UQ*) session for the six patients with positron emission tomography brain imaging.

pleted the PET of brain study reported an increase in tinnitus or a subjective loss of hearing.

Complications

No patient reported additional subjective hearing loss or increase of the tinnitus (or both) with UHF/UQ therapy before or after the PET examinations.

DISCUSSION

This study is the first known nuclear medicine imaging study reporting the use of PET of brain in SIT patients in an attempt to apply UHF/UQ stimulation for tinnitus relief. The three metabolic categories of brain PET—hyperactivity, hypoactivity, and mixed activity (see Fig. 3)—identified in individual ratios before and after UHF/UQ stimulation in multiple ROI are clinically considered to reflect differences in cortical neuronal reorganization. The consistency of the PET response in the selected ROI suggests a neuronal pathway for the tinnitus signal or the UHF/UQ stimulus (or both).

Our discussion focuses on the highlights of the PET study: metabolic categories of brain PET after UHF/UQ; the cerebellum; UHF audiograms; MMLs; behavior responses; and questions of underlying mechanisms of hearing, masking, and tinnitus production.

PET of Brain Data

The finding of lack of random response in individual analyses of the ratios of post- and pre-UHF/UQ in any of the PET of brain ROI selected for analysis is significant. The PET of brain findings provide objective evidence for the efficacy of UHF/UQ in providing tinnitus relief and support the proposition of a neurophysiological component to tinnitus relief. Owing to the small sample size, we were not able to separate the patients into groups on the basis of their level of relief from tinnitus and to determine whether a significant difference could be detected in their individual PET recordings. The only ROI that demonstrated a common asymmetry in all patients was in the cerebellum. The PET of brain findings support the results of an interneuronal network activation in tinnitus patients as reported in previous SPECT of brain imaging studies [1–6,18].

The three metabolic categories of PET of brain after UHF/UQ stimulation are considered to reflect the already reported varying degrees of neural reprogramming-reorganization secondary to peripheral hearing loss [19]. Reorganization of the auditory cortex in tinnitus patients has demonstrated an expansion in the tinnitus frequency area (more than doubled in size), with a

suggestion of lower-frequency expansion below the expected frequency subsequent to the hearing loss [20].

Cerebellum

The PET of brain finding of cerebellum involvement supports the hypothesis of involvement of the acoustic motor pathway in tinnitus patients (see Fig. 5) [18]. The frontal lobe and cerebellum ROI demonstrated the highest ratio of change before and after UHF/UQ stimulation. The reported PET findings of alterations in metabolism in multiple ROI of brain are consistent with the original SPECT of brain findings in SIT patients (i.e., a reciprocal, interactive, interneuronal network reflecting brain function in tinnitus patients) [1–5,18].

The identification with PET of brain of metabolic alterations in multiple ROI in brain involved with tinnitus supports the concept and findings reported initially with SPECT of brain of multiple ROI other than and in addition to the auditory cortex involved in tinnitus [1].

The high degree of consistency and the absence of random response for the three categories of metabolic response for the selected ROI support consideration of an underlying interneuronal network of activity in SIT patients in multiple ROI or a questionable pathway for both tinnitus and the UHF/UQ stimulation. We consider the finding of statistical significance in the cerebellum in this study to reflect clinically the involvement of the acoustic motor pathway (i.e., integration of sensory and somatosensory components of the tinnitus complaint) [18].

One consideration is that PET of brain metabolic categories support the hypothesis that the UHF/UQ provides a bone conduction signal that exerts a bilateral effect on the inner ear and a direct vibratory stimulation via "fluid channels" to the entire brain. The mechanism of detecting bone- and fluid-conducted ultrasound is likely related to a single demodulating system. We hypothesize this system to be the brain. More efficient high-fidelity, high-frequency stimulation is obtained with the UHF/UQ system than is possible by air conduction hearing [8,9].

The PET categories of response are considered to support the proposition that the application of high audio frequencies (>10 kHz) to the skull by bone conduction may produce "masking" in frequencies corresponding specifically to the brain's resonant frequency (approximately 15 kHz) [8]. Ultrasonic masking has been reported to suppress audio thresholds in the 8- to 12.5-kHz range by 2–29 dB [21,22]. The maximum ultrasonographic masking effect was reported in a 12.5- to 16-kHz range and less for frequencies higher and lower than the resonance peak characteristic for a resonance phenomenon [8]. The principle factor is not the

relative energy but its relationship to the fundamental frequency of the forced brain in motion [8].

UHF Audiograms and PET of Brain Metabolic Category

Correlation of the PET data from the six patients with the UHF audiograms revealed that the best clinical subjective report of reduction in severity (in two patients) was in the hypoactive metabolic PET category and that the UHF audiometric thresholds were 40–50 dB SPL or less in the frequency range of 10–14 kHz (see Tables 1, 2; see Figs. 1, 2, 4). Furthermore, the remaining two metabolic categories correlated with the residual neuronal function as revealed in the UHF audiograms and the reported tinnitus relief. Specifically, patients in the hyperactive metabolic PET category (n = 3) reported a tinnitus severity reduction lower than those in the hypoactive metabolic PET category and had audiometric UHF thresholds greater than those in the hypoactive metabolic group (i.e., audiometric thresholds of 50–60 dB SPL or more in the frequency range of 10–14 kHz).

The one patient in the mixed PET of brain metabolic category (i.e., between the hypoactive and hyperactive metabolic categories) demonstrated "borderline" (40–50 dB SPL) UHF audiometric thresholds for the frequency range of 10–14 kHz. The outcome in the one patient in the mixed category is considered to support the clinical significance of the correlation of the brain PET of brain metabolic categories and the UHF audiogram. Specifically, the audiometric thresholds of response for the mixed category are for the right ear (between 20 and 40 dB SPL for the frequencies of 10–12 kHz and between 60 and 80 dB SPL for 11–14 kHz). For the left ear, the audiometric thresholds were reduced overall (i.e., 40–50 dB SPL at 12 kHz, and below 40–50 dB SPL for the frequencies of 13–14 kHz; see Table 1; see Fig. 4). One can clinically consider a "balance" to have occurred at the periphery between the inputs from left and right ears, which then was projected to the brain cortex and was identified with "mixed" plots of brain PET metabolic counts (i.e., not predominantly hyper- or hypometabolic). The clinical response of this tinnitus patient in the brain PET mixed metabolic category was one of the best for tinnitus efficacy with UHF/UQ. We considered the UHF audiogram of that patient to support further the clinical impression that the UHF/UQ is most effective in SIT patients with a UHF audiometric threshold of response between 40 and 50 dB SPL or less for the UHF frequencies of 10–14 kHz.

Correlation of the three metabolic categories of brain PET response with the UHF audiogram is hypothesized to reflect a dual effect (i.e., in the periphery) of

the response of the number of residual functioning neurons in the UHF range at the basilar membrane in the cochlea, specifically the 10- to 14-kHz range, and at the cortex of neural reprogramming and reorganization. The integrity of the brain cortex is critical for plastic changes involving neural reprogramming and neural reorganization. The presence of a greater number of residual neurons in the UHF at the 10- to 20-kHz range is considered to require a lower threshold of acoustic stimulation to respond (i.e., require less acoustic energy), which is reflected centrally for neural reprogramming and reorganization at brain cortex as a metabolic hypoactivity. The category of metabolic hyperactive brain PET in tinnitus patients (n = 3) is clinically considered to reflect a reduced number of residual neurons in the UHF range of 10–20 kHz; they require more acoustic energy for activation and therefore reflect as a metabolic hyperactivity at brain cortex. The one patient in the mixed category significantly revealed a UHF audiogram considered to be "borderline" for tinnitus relief with UHF/UQ at the frequencies of 10–14 kHz, with audiometric thresholds on or about 40–50 dB SPL.

Although this PET sample size (n = 6) is small, the correlation of the three PET categories of response with the UHF audiogram and the subjective scale of efficacy for the UHF/UQ supports our ongoing clinical experience for patient selection for establishing tinnitus control with UHF stimulation: that is, the best SIT patient selected for attempted tinnitus relief with UHF/UQ has demonstrated a UHF audiometric threshold of 40–50 dB SPL or less in the frequency range of 10–14 kHz (see Figs. 1, 2) [12–15].

Behavior Outcomes

Attempts to correlate the subjective behavioral responses of tinnitus patients for UHF tinnitus relief included questionnaires for tinnitus intensity and annoyance and the TSI. The results of the behavioral correlation have been reported for the total cohort (N = 15) [11–15]. The PET of brain metabolic categories of response correlated with the feedback from the behavioral questionnaires of tinnitus intensity and annoyance and the TSI and with the subjective scale of efficacy of the UHF/UQ device as reported by the patients (see Table 2). Specifically, the best SIT responses were in the hypoactive metabolic PET of brain category (i.e., where the UHF audiogram met the criteria of the 40- to 50-dB or less audiometric threshold in the 10- to 14-kHz frequency range). Patients in the hyperactive metabolic brain PET category revealed a reduced correlation with tinnitus relief (i.e., a poor UHF audiogram: audiometric thresholds >40–50 dB SPL for frequency ranges of 10–14 kHz). The one patient in the PET of brain mixed

metabolic category reported tinnitus relief as a reduction in annoyance. We noted a consistency in the report of tinnitus relief for severity mostly in the hypoactive metabolic brain PET category (see Figs. 4, 6).

Correlation of the PET of brain metabolic categories with the TSI results revealed a significant improvement and a tendency to response latency for tinnitus relief in comparing 1 week to 8 weeks of the UHF/UQ stimulation. Tinnitus intensity and annoyance demonstrated fluctuation (see Table 2; see Fig. 6) [11–15].

The latency in tinnitus relief reported by some patients (see Fig. 6) at the end of the first and 8 weeks of stimulation is considered clinically to reflect a differential rate of progressive neural reprogramming (individual) and is based on two factors: (1) the peripheral residual high-frequency neuronal function and (2) the integrity of the brain cortex (i.e., the degree, if any, of damage at a cortical level interfering in neural reprogramming and reorganization) (see Tables 1, 2; see Fig. 6).

Results of patients' subjective evaluation of the efficacy of the UHF/UQ device for tinnitus relief demonstrated individual variability. Overall, in this limited PET of brain study, this outcome did not correlate with the reported decrease in intensity (i.e., TSI; see Table 2). We suggest that although the UHF/UQ may provide tinnitus relief as reported by tinnitus patients, patients may not "want" or "like" this device. This finding is similar to our clinical experience with tinnitus acoustic masking attempting tinnitus relief and the hearing aid recommendation for attempting improvement in hearing and tinnitus relief [16]. This finding supports the clinical experience that treatment options differentiate between what is recommended for the sensory and affect components of the symptom of tinnitus [17].

Hearing

No subjective hearing loss was reported by any of the study's six patients [11–15]. Potential damage (e.g., high-frequency hearing loss and tinnitus) has been reported in listening to intense, head-coupled ultrasonic stimulation, which suggests a dynamic mechanism that is a function of the remaining hair cells and intensity of the ultrasonic stimulation [23]. We consider this PET of brain study to contribute to an understanding of underlying mechanisms involved in UHF/UQ acoustic stimulation and its application for tinnitus control.

Questions

Questions that have arisen from this study as a result of the PET of brain findings and that remain to be answered to explain the reported tinnitus relief with

UHF/UQ therapy include those of masking, acoustic space mapping, and structure of the neural code.

1. Is the UHF/UQ acoustic stimulus a "masking" signal? Is the masking effect with UHF/UQ similar to or different from that resulting from classic acoustic stimulation? What is the site of action of the UHF/UQ stimulus: peripheral, central at brain cortex, or both?

Also to be considered is that the mechanism underlying the masking effect with UHF/UQ may not be the same as that with classic acoustic audio frequencies in the 250-Hz to 8-kHz range. The masking phenomenon of the auditory system is conceived to have different generators at different levels of the ascending and descending auditory system, with involvement of different and multiple neurotransmitter systems.

The PET of brain data suggest that the "masking" for perception of UHF frequencies is a different mechanism from that of "masking" from classic conventional audio frequencies. The role of brain demodulation for sound perception and attempted tinnitus relief is suggested to be unique for UHF and introduces concepts new to that of classic acoustic masking [24].

The PET categories of metabolic response and their correlation with the UHF audiometric responses support the suggestion that the "masking" effect may be predominantly cortical and is reflected in cortical neural reorganization and reprogramming. We consider a predominantly cortical effect to be supported by the lack of correlation of the PET of brain metabolic categories of response and the Feldmann masking curves (see Table 2). The Feldmann masking curves are clinically considered to reflect a masking response, predominantly in the cochlea, of residual functioning neurons at the basilar membrane between the frequencies of 250 Hz and 8 kHz. The "masking" effect with UHF/UQ suggests consideration of different loci and mechanisms for masking (i.e., classic acoustic, electrical, UHF, and ultrasonic frequencies, as well as other types of stimulation of the brain and cochleovestibular system). Furthermore, that classic conventional acoustic stimulation (250 Hz–8 kHz) is different from the "masking" achieved with UHF masking.

In classic masking, a noise band is effective generally if it overlaps with the sound to be masked [24]. An exception is the case of upward spread of masking when a low tone at a certain intensity can mask a tone much higher in frequency. In our study, MMLs were reduced across the audiometric range (250 Hz–8 kHz), varying individually by degree. Thus, UHF therapy had a downward-spread effect on the lower frequencies. Of course, UHF is not masking in the sense that it is not applied simultaneously in MML testing. This all is consistent with a central masking process. Possibly, multiple levels in the auditory neuraxis are involved. UHF could

activate the olivary system, changing the afferent output of the cochlea, or plasticity in neural responses could change from the thalamus through the cortex [9,10].

The MML alterations varied in different degrees for each of the three PET of brain metabolic categories of response (see Table 2). The most significant alteration in MMLs (i.e., reduction in masking level [dB]) was in the PET of brain hypoactive metabolic category. One can hypothesize that the MML variations after UHF/UQ stimulation will reflect the number of residual neurons in the cochlear range (10–20 kHz), requiring acoustic threshold intensity of 40–50 dB SPL or less for activation. The correlation of PET of brain data and the MMLs suggests that the masking mechanisms with UHF/UQ frequencies is different from masking mechanisms achieved with classic acoustic frequencies (i.e., 250 Hz–8 kHz).

2. Does the UHF/UQ stimulus stimulate only the brain and not the residual UHF frequencies in the cochlea or both? How does electrical stimulation achieved with a bone-conducted stimulus differ from UHF/UQ stimulation, if at all?

It is hypothesized that UHF/UQ stimulates the cochlea and the brain. The UHF/UQ sets the brain in motion. Brain demodulation results in neural reprogramming and reorganization at a cortical level in multiple areas of cortex, which, when successful, masks the tinnitus and is reported by tinnitus patients as tinnitus relief [8,9]. We suggest that differentiation be made among classic acoustic masking, UHF/UQ masking, and electrical masking.

Alterations in the MMLs (see Table 2) and their correlation with the PET categories of response suggest a new concept of masking for UHF/UQ other than that of classic acoustic masking at 250 Hz–8 kHz (i.e., the substitution of one sound for another). Similarly, our experience with attempting electrical suppression for tinnitus relief suggested that "electrical masking" was different from classic acoustic masking at 250 Hz–8 kHz. Electrical masking was hypothesized to explain electrical suppression of tinnitus (G. McCandless, personal communication) [25].

Nuclear medicine imaging in general and demonstrated with PET of brain in this study provides a means to identify underlying molecular genetic and neurochemical mechanisms—individual or shared (or both)—that are involved in the masking effect of a given masking signal in attempting tinnitus relief. A preliminary report of the application of magnetoencephalography to try to establish electrophysiological evidence of classic acoustic masking has reported involvement of the temporal lobe [26].

3. What are the meaning and significance of the images of the present PET of brain imaging study intro-

duced to objectify and monitor the UHF/UQ stimulation in attempting tinnitus relief?

It is suggested that the ROI selected for examination with PET of brain in this study reflect an auditory space map in tinnitus patients exposed to UHF/UQ. Whether the metabolic function in these ROI, as demonstrated with PET of brain, reflects the tinnitus signal or that of the UHF stimulus or both remains for future investigation.

We suggest that the PET of brain metabolic categories reflect (1) the response at brain cortex of the input from the spread of the displacement in the basilar membrane to the remaining intact UHF hair cells in response to UHF/UQ acoustic stimulation and (2) the metabolic correlate of neuronal programming at brain cortex. Cortical neural reprogramming depends on the integrity of the brain cortex . For example, the presence of central nervous system disease, particularly cerebrovascular disease, may influence or interfere in both neural reprogramming at brain cortex in response to UHF/UQ stimulation and resultant tinnitus relief.

This PET of brain study demonstrates the involvement of multiple ROI in the brain in tinnitus patients, not only in the auditory cortex. The role of the auditory cortex in auditory space mapping occurs in the process of identification [27]. The PET of brain data support the view that the function of the auditory cortex is dynamic and not stable. Homeostatic synaptic stability is considered crucial for activity-dependent stabilization of the neural circuits [28]. The auditory cortex constantly responds with a reorganization response to an experience for a sensory task to receive relevant stimuli [29,30]. The PET of brain data in this study are considered to reflect this alteration in multiple areas of brain, including the auditory cortex, resulting from an aberrant stimulus (i.e., tinnitus or UHF stimulation, or both).

Variations in degree and duration of tinnitus control with UHF/UQ may reflect a preexistent alteration in the integrity of the brain cortex, which may interfere in neural reorganization in the auditory cortex. A subset of a large population of neurons has been reported to respond to the auditory stimulus frequency (i.e., UHF/UQ) [8,9].

Observed electrophysiological cortical changes have been linked in animal experiments to behavior [30,31]. Our UHF/UQ PET study raises a question: Was the subjective behavioral response of tinnitus relief the cause of the metabolic change in brain cortex as reflected in the PET of brain metabolic categories reported or did the absence of cortical reorganization result in the behavioral response of less tinnitus relief? Again, the question arises: If residual central nervous system cortical damage exists in a particular tinnitus patient, how may it influence cortical reorganization and response to UHF stimulation or to other modalities attempting tinnitus

relief? Our study suggests a direct cortico-cortical modulation pathway with activation of the auditory cortex by the UHF/UQ or subcortical input and interneuronal inputs from other ROI.

4. Is the tinnitus relief from the UHF/UQ stimulus a true "masking effect" or is the reported tinnitus relief a behavioral response? What are the meaning and clinical significance of the PET of brain images? Are the PET of brain metabolic categories of tinnitus relief the behavioral response of SIT patients and thus do they reflect the neuronal reorganization at brain auditory cortex and associated ROI in brain that has actively tuned itself to a newly acquired stimulus (UHF/ UQ)? Is the variation in the reported degree of tinnitus relief in the ROI a clinical reflection of a sensory-affect transformation of an aberrant auditory sensory stimulus hypothesized to occur in a final common pathway not only for the aberrant auditory stimulus tinnitus but for all sensations?

Our PET of brain study with UHF/UQ stimulation and its associations with sensory parameters of tinnitus intensity, severity, and the affect parameters of annoyance and subjective evaluation of the UHF/UQ device is clinically considered to demonstrate the reported different components—sensory and affect—of the symptom of tinnitus. The transition between the two is hypothesized to occur in a final common pathway for tinnitus. We suggest that the integrity of this pathway influences not only the individual response to a sensation but the behavioral response. We further consider the results of this brain PET study with UHF/UQ to support the hypothesis of a final common pathway for tinnitus [5].

The problem one faces with the clinical interpretation of the PET of brain data is that it is limited to six SIT patients and that the organization of the cortical auditory system is still controversial in 2004 [32]. The PET of brain data of this study contribute to basic science questions in systems neuroscience of the structure of the neural code [33]. The PET of brain metabolic categories of response in this study contribute to an understanding of this issue. Tinnitus, an aberrant auditory stimulus, is hypothesized to reflect a dysynchrony within the cochlear vestibular system, which clinically is manifested with the significant behavioral response (e.g., anxiety, depression) [17,25]. Also to be considered are recent reports that coding and transmission of information by neural ensembles involve complex temporal dynamics that characterize cortical function. When oscillation of neurons is coherent rather than noise, the result is a "normal" flow of information [33]. In our study, the absence of random activity in the ROI of brain suggests a coherence in oscillation at brain cortex that is variable, as reflected in the metabolic

categories of PET of brain. The variabilities in coherence are clinically considered to have been identified by the three PET of brain metabolic categories of response to the UHF/UQ and are also associated with the individual degrees and latency of occurrence of reported tinnitus relief, a behavioral response.

Whether regional specialization occurs in cortical processing of a complex sound is unclear [32]. Imaging goes beyond investigations of the cortical auditory system with electrophysiological recordings. The symptom of tinnitus and sensory disorders requires a synergy between electrophysiology and nuclear medicine imaging to correlate and identify findings for understanding underlying mechanisms and neurochemistry involved in brain structure and function. In our study, the PET of brain data are considered to provide a "road map" for neurophysiologists to investigate not only the tinnitus signal but the pathway of the UHF/UQ. The ROI identified suggest that areas other than that of the auditory cortex have to be investigated in all tinnitus patients using different modalities of therapy and techniques. Techniques other than PET to be considered for investigation include cytoarchitecture; histochemical procedures [34–36]; tract-tracing studies [37,38]; and fMRI, electroencephalography, magnetoencephalography, 2-deoxyglucose autoradiolucency [39], and optical imaging [40–42]. Our PET study reinforces the need for future studies that go beyond investigation of the primary auditory cortex for auditory processing of the tinnitus signal but also of that of modalities of therapy attempting tinnitus relief [1–5,18].

Distinct pathways for processing different aspects of acoustic stimuli that have been proposed are analogous to the functional streams proposed in visual cortex (i.e., dual processing streams) [43–45]. It is suggested that the PET results may reflect an anteriorly directed "what" pathway of the sensory stimulus and a posteriorly directed "where" pathway—both of which may have application for auditory processing. The activation of different cortical areas is reported to have behavioral consequences of reversibly inactivating different cortical areas [30,31]. Investigations have placed emphasis on the correlation between auditory signals and speech processing in acoustic processing. Integrating such reports with results of nuclear imaging studies in severely disabled tinnitus patients is necessary.

The use of UHF/UQ in this PET of brain study, although limited to six SIT patients, may provide such a start for understanding the auditory space map of the tinnitus signal. Our PET study provides a method for quantifying brain function in multiple ROI rather than only in a single area (i.e., the primary auditory cortex). This study reinforces the need not only for bottom-up but for top-down imaging studies in SIT patients. Tinnitus provides a unique opportunity to understand an aberrant sensory stimulus and its behavioral consequences. Nuclear medicine brain imaging provides a basis for asking the right questions that may contribute to understanding the final common pathway for tinnitus and the ultimate improvement in the clinical diagnosis and treatment methods not only for tinnitus but for all sensory phenomena.

SUMMARY AND CONCLUSIONS

No patient reported a subjective increase in hearing loss, tinnitus, or imbalance after UHF/UQ therapy and pre– and post–PET brain scanning. PET of brain, a nuclear medicine imaging technique, has in this study provided an objective, quantitative, noninvasive measure of the efficacy of a modality of therapy attempting tinnitus relief (UHF/UQ stimulation). The PET of brain data and the degrees of tinnitus relief—ranging from very good to fair— from UHF/UQ correlated with three PET categories of metabolic response in brain cortex.

The PET of brain metabolic categories of response have demonstrated a correlation among residual peripheral UHF neuronal function; subjective outcomes questionnaires of tinnitus intensity; MMLs; the TSI; annoyance; and subjective behavioral reports of tinnitus relief. We believe that the PET results support our hypothesis that UHF/UQ brain demodulation with neural reorganization occurs in multiple cortical areas, resulting in tinnitus relief. The PET of brain categories of metabolic response with UHF/UQ demonstrated the significance for tinnitus relief of residual functioning UHF neurons for tinnitus relief (i.e., 40–50 dB SPL audiometric thresholds for frequencies of 10–14 kHz). We suggest UHF audiometric testing for tinnitus patient selection when attempting UHF/UQ stimulation for tinnitus relief.

ACKNOWLEDGMENTS

REFERENCES

1. Shulman A, Strashun AM, Afriyie M, et al. SPECT imaging of brain and tinnitus—neurotology neurologic implications. *Int Tinnitus J* 1(1):13–29, 1995.

2. Shulman A, Strashun AM, Seibyl JP, et al. Benzodiazepine receptor deficiency and tinnitus. *Int Tinnitus J* 6(2):98–111, 2000.

3. Shulman A, Strashun AM, Goldstein BA. GABA$_A$-Benzodiazepine-chloride receptor-targeted therapy for tinnitus control: Preliminary report. *Int Tinnitus J* 8:30–36, 2002.

4. Daftary A, Shulman A, Strashun AM, et al. Benzodiazepine receptor distribution in severe disabling tinnitus. *Int Tinnitus J* 10(1):17–23, 2004.

5. Shulman A. A final common pathway for tinnitus—medial temporal lobe system. *Int Tinnitus J* 1:115–126, 1995.

6. Shulman A, Goldstein BA. A final common pathway for tinnitus—implications for treatment. *Int Tinnitus J* 2(3):137–142, 1996.

7. Meikle MB, Edlefson LL, Lay JW. *Suppression of Tinnitus by Bone Conduction of Ultrasound*. Presented at the Twenty-First Annual Meeting of the Association for Research in Otolaryngology, St. Petersberg, FL, 1999.

8. Lenhardt ML, Skellet R, Wang P, Clarke A. Human ultrasonic speech perception. *Science* 253:82–85, 1991.

9. Lenhardt ML. Ultrasonic hearing in humans: Applications for tinnitus treatment. *Int Tinnitus J* 9(2):69–75, 2003.

10. 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.

11. Shulman A, Strashun AM, Avitable MA, et al. *Ultra High Frequency Stimulation and Tinnitus Relief*. Presented at the Neurootological and Equilibriometric Society meeting, March 24, 2004, Bad Kissingen, Germany.

12. Goldstein BA, Shulman A, Lenhardt ML, Guinta R. Ultra high frequency stimulation and tinnitus relief—short- and long-term results. Presented at the International Tinnitus Forum, September 20, 2003, Orlando, FL.

13. Shulman A, Goldstein BA. *Ultra High Frequency Stimulation for Tinnitus Relief—Patient Selection*. Presented at the Neurootological and Equilibriometric Society meeting, March 24, 2004, Bad Kissingen, Germany

14. Shulman A, Strashun AM, Avitable MA, et al. *Ultra High Frequency Stimulation and Tinnitus Relief—A PET Study*. Presented at the Neurootological and Equilibriometric Society meeting, March 24, 2004, Bad Kissingen, Germany.

15. Shulman A, Goldstein BA. *Ultra High Frequency Stimulation for Tinnitus Relief—Patient Selection*. Presented at Charles University, Department of Otolaryngology, Prague, Czech Republic, March 28, 2004.

16. Shulman A. Medical audiological evaluation of the tinnitus patients. *Semin Hear* 8(1):7–14, 1987.

17. Shulman A, Tonndorf J, Feldmann H, et al. *Tinnitus Diagnosis Treatment*. Philadelphia: Lea & Febiger, 1991.

18. Shulman A, Strashun AM. Descending auditory system/cerebellum/tinnitus. *Int Tinnitus J* 5(2):92–106, 1999.

19. Schwaber MK, Garaghty PE, Kaas JH. Neuroplasticity of the adult primary auditory cortex following cochlear hearing loss. *Am J Otol* 14:252–258, 1993.

20. Muhlnickel W, Ebert T, Taub E, Flor H. Reorganization of the auditory cortex in tinnitus. *Proc Natl Acad Sci USA* 95:10340–10343, 1998.

21. Kono S, Suzuki Y, Sone T. Some considerations on the perception of ultrasound and its effect on hearing. *J Acoust Soc Jpn* 6(1):1–9, 1985.

22. Nishimura T, Nakagawa S, Sakaguchi T, Hosai H. Ultrasonic masker clarifies ultrasonic perception in man. *Hear Res* 175(1–2):171–177, 2003.

23. Deatherage BH, Jeffress LA, Blodgett HC. A note on the audibility of intense ultrasound. *J Acoust Soc Am* 26:582, 1954.

24. Tonndorf J. A new concept of bone conduction. *Arch Otol* 87:49–54, 1968.

25. Shulman A, Tonndorf J, Feldmann H, et al. *Tinnitus Diagnosis Treatment. Electrical Stimulation*. Philadelphia: Lea & Febiger, 1991:514–531.

26. Van Marle HJF, Kronberg E, Schulman JJ, et al. Magnetoencephalographic Recordings from Tinnitus Patients During Masking Procedures. In H Novack, F Geissler, R Huonker (eds), *BIOMAG 2002*. Berlin: VDE Verlag, 2002:191.

27. Middlebrooks JC. The acquisitive auditory cortex. *Nat Neurosci* 6(11):1122–1123, 2003.

28. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nat Neurosci* 5:97–107, 2004.

29. Surmeir DJ, Foehring R. A mechanism for homeostatic plasticity. *Nat Neurosci* 7(7):691–692, 2004.

30. Fritz J, Shamma S, Elhilali M, Klein D. Auditory cortical reorganization. *Nat Neurosci* 6:1216–1223, 2003.

31. Fritz J, Shamma S, Elhilali M, Klein D. Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex. *Nat Neurosci* 6:1216–1223, 2003.

32. Griffiths TD, Warren JD, Scott SK, et al. Cortical processing of a complex sound: A way forward? *Trends Neurosci* 27(4):181–185, 2004.

33. Averbeck BB, Lee D. Coding and transmission information by neural ensembles. *Trends Neurosci* 27(4):225–230.

34. Wallace MN, et al. Histochemical identification of cortical areas in the auditory region of the human brain. *Exp Brain Res* 143:499–508, 2002.

35. Zilles K, et al. Architectonics of the human cerebral cortex and transmitter receptor fingerprints: Reconciling functional neuroanatomy and neurochemistry. *Eur Neuropsychopharmacol* 12:587–599, 2002.

36. Padberg J, et al. Architectonics and cortical connections of the upper bank of the superior temporal sulcus in the rhesus monkey: An analysis in the tangential plane. *J Comp Neurol* 467:418–434, 2003.

37. Romanski JM, et al. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci* 2:1131–1136, 1999.

38. Huang CL, Winer JA. Auditory thalamocortical projections in the cat: Laminar and areal patterns of input. *J Comp Neurol* 427:302–331, 2000.

39. Poremba A, et al. Functional mapping of the primate auditory system. *Science* 299:568–572, 2003.

40. Versnel H, et al. Optical imaging of intrinsic signals in

ferret auditory cortex: Responses to narrow band sound stimuli. *J Neurophysiol* 88:1545–1558, 2002.

41. Rinne T, et al. Scalp recorded optical signals make sound processing in the auditory cortex visible? *Neuroimage* 10:620–624, 1999.

42. Bizley JK, et al. An Investigation into the Functional Anatomy of the Ferret Auditory Cortex Using Optical Imaging and Multielectrode Recordings. Program No. 354.1. *Abstract Viewer and Itinerary Planner*. Society for Neuroscience. CD-ROM (2002).

43. Belin P, Zatorre RJ. 'What,' 'where,' and 'how' in auditory cortex. *Nat Neurosci* 3:965–966, 2003.

44. Raushecker JP, Tian B. Mechanisms and streams for processing the "what" and "where" in auditory cortex? *Proc Natl Acad Sci USA* 97:11800–11806, 2000.

45. Lomber S, Malhotra S. Double Dissociation of "What" and "Where" Processing in Auditory Cortex. Program No. 488.8. *Abstract Viewer and Itinerary Planner*. Society for Neuroscience. Online, 2003.