International Tinnitus Journal, Vol. 5, No. 1, 5–15 (1999)

# A Tinnitus Objectivization: How We Do It

**Dunja Milicic[1] and Manuel N.M.P. Alçada[2]**

[1]*Department of Otorhinolaryngology, Hospital São João, Medical School, Porto, Portugal, and*
[2]*Department of Biochemistry, Medical School, Porto, Portugal*

***Abstract:*** The medical therapy of tinnitus should be oriented by objective measurement of the disorder. Preferably, it should be qualitative, indicating the exact neural mechanism to be neuromodulated by neuroprotective medication. The neurophysiological approach in objectivization of tinnitus is presented by means of auditory brainstem response and middle latency response. These tests could be applied in functional follow-up of medical therapy, as these are more sensitive and harmless methods as compared to standard morphological methods.

***Keywords:*** auditory brainstem response; middle latency response; qualitative objectivization; tinnitus

The exact approach to medical treatment of tinnitus should be on the basis of neuromodulation by neuroprotective drugs. This approach is defined extensively in the work of Dr. A. Shulman, on the basis of current knowledge of tinnitus, with all its implications and with a final goal of at least controlling, if not curing, tinnitus [1].

In recent literature, various therapeutic modalities were presented, based principally on empirical results [2–9]. Even though the value of these results is undisputed, we are faced with a certain sensation of "insecurity." In that "blind" period, before the possibility of determining whether therapy is effective, we are confronted with several dilemmas: the correct choice of medication, following the principle "Primum nil nocere," and the possibility of under- or overmedicating. A financial loss, a loss of time, a loss of self-confidence, and a loss of positive patient's transfer are possible.

The need for standardization in this area has already been stressed [10]. The objectivization of tinnitus with an exact identification of a dysfunction is needed. Some quantitative identification could be obtained with standard audiological techniques. Nonetheless, we still lack so much necessary information about the location and the type of dysfunction underlying this auditory symptom.

Reprint requests: Dunja Milicic, Rua da Constituição, 1497–4° Esq, 4200 Porto, Portugal. Phone: 2-810805.
This work was presented at I Curso de Zumbidos/Diagnostico e Tratamento, Porto, Portugal, June 25–27, 1997.

The qualitative identification of dysfunction (excitatory or inhibitory) should be the determining factor in selecting medication. The type of dysfunction indicates the exact mechanism with which therapy should interfere. The excitoxicity [1], primarily of glutamate [1,3,11], with intracellular $Ca^{++}$ overload [1,12–14] leading to cellular death has been demonstrated [15]. Intervention in the earliest possible phase of neurotoxicity is preferable [1].

Recently, single-photon emission computed tomography (SPECT) of brain [10], functional magnetic resonance imaging (fMRI) [16,17], and magnetoencephalography [18,19] are powerful tools in objective measurement of tinnitus, affording us the possibility to visualize the alteration. In our opinion, tinnitus is primarily an acoustic phenomenon. It is a neural, receptor-dependent dysfunction, an afferent depolarization pattern that mimics sound-induced patterns, subjectively perceived as tinnitus and independent of possible accompanying hearing loss [20]. Its generation should be near the auditory afferent (AA) pathway [20], possibly the specific tinnitus pathway [21]. SPECT and fMRI are, by definition, indirect and delayed evaluative methods and provide a representation of underlying activity (metabolic or hemodynamic) [17]. Though these activities might be overlapping, they are not those specific qualitative alterations of neural-electrical activity that we want to register.

Because SPECT and fMRI were not available to our patients, we were obliged to use a method that would objectively assess tinnitus in our patients. Our option was neurophysiology: specifically, auditory brainstem response (ABR) and middle latency response (MLR).

The ABR is a well-known neurophysiological test, included in almost every battery of tests but proving to be minimally efficient [22]. The MLR is a neural auditory response that provides a representation of activity of thalamocortical projections [23] (predominantly temporal in adults [24]) and the reticular activating system [25], as well as nonprimary divisions of the AA pathway [26], processing multisensory stimuli [27]. Its trajectory could overlap particularly with projections involved in tinnitus generation [21], including the Jastreboff model [28].

## OUR TECHNIQUE: A CASE REPORT

HHCR is a male, right-handed, 19-year-old student. In infancy, he was followed up for ventilation dysfunction of the left ear. Otherwise, he was healthy. In November 1997, he was hospitalized in a psychiatric institution for hypochondria and psychotic alterations of personality. His unique and persistent complaint was tinnitus in the right ear.

### First Observation

On December 3, 1997, he was oriented to the department of otorhinolaryngology (ORL), Hospital São João, Medical School, University of Porto, Portugal. The ORL examination was normal, except for an allergic, nonsymptomatic rhinitis and nasal septal deviation to the left.

Sudden-onset tinnitus occurred in the right ear. It was continuous, lasting several months. Frequency and intensity were stable and very incapacitating. The patient expressed no other ORL complaints. Tonal audiometry with the identification of tinnitus is demonstrated in Figure 1. No hearing loss was found. Tinnitus had characteristics of a pure tone with an intensity of 40 dB HL (25 dB sensational level), with a frequency of 2,000 Hz in the right ear.

Tympanometry was symmetrical, bilateral type A, with less compliance in the left ear. Stapedial reflex was absent on ipsilateral and contralateral stimulation bilaterally. The stapedial tone-decay test was neural on the right side for all frequencies (500, 1,000, 2,000, and 4,000 Hz). On the left side, it was normal at 500 Hz and neural at other frequencies. No other neurootological alterations were found.

#### *Neurophysiological Testing*

The recording was performed with a Nihon Kohden, Neuropack 8, MEB 4200K with four channels. The ABR and MLR stimulation were performed by an MS-411B Auditory-Visual Stimulator Unit with headphones DR-531B7. The recordings were performed in an acoustically and electrically shielded room, on an unsedated, semireclining patient.

Standard Ag/AgCl disc electrodes were located on vertex (+), and referred to the ear lobe of the stimulated ear (−), and contralateral ear (−). The forehead electrode served as a ground. The skin was cleansed with Nihon Kohden Skinpure, and electrodes were fixed with Nihon Kohden EEG paste (Elefix). Skin resistance did not exceed 2 kΩ.

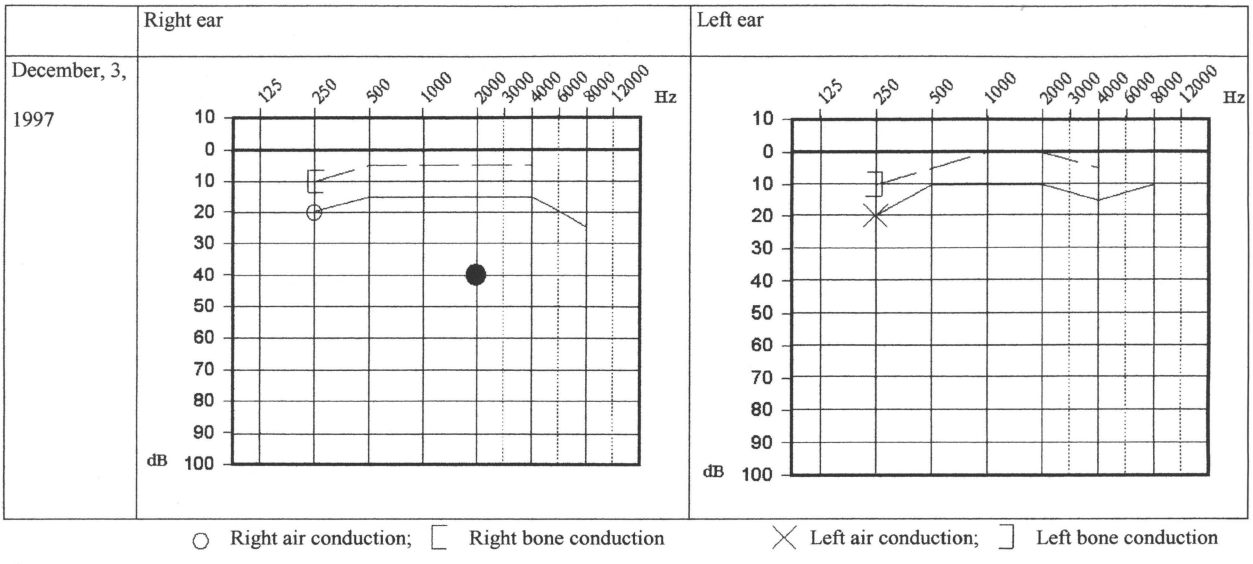



**Figure 1.** Hearing threshold level and tinnitus identification on December 3, 1997, on patient HHCR, male, 19 years old.

The ABR analysis time was 10 msec, sweep rate (pulses per second [PPS]) 21 and 71; sweep count, 2,048; low-frequency cut-off, 100 Hz (roll-off, 12 dB/octave); high-frequency cut-off, 2,000 Hz (roll-off, 12 dB/octave). The MLR analysis time was 100 msec; sweep rate, 9; sweep count, 1,024; low-frequency cut-off, 20 Hz (roll-off, 12 dB/octave); high-frequency cut-off, 100 Hz (roll-off, 6 dB/octave). Stimulation for ABR was accomplished with an alternating click of 0.1-msec duration and 100-dB sound pressure level intensity. For MLR, it was accomplished with a tone burst of 500-Hz frequency, with a rise-fall time of 0.5 msec, a plateau time of 4 msec, and an intensity of 100-dB sound pressure level. Stimulation was monaural, and recording was ipsilateral and contralateral.

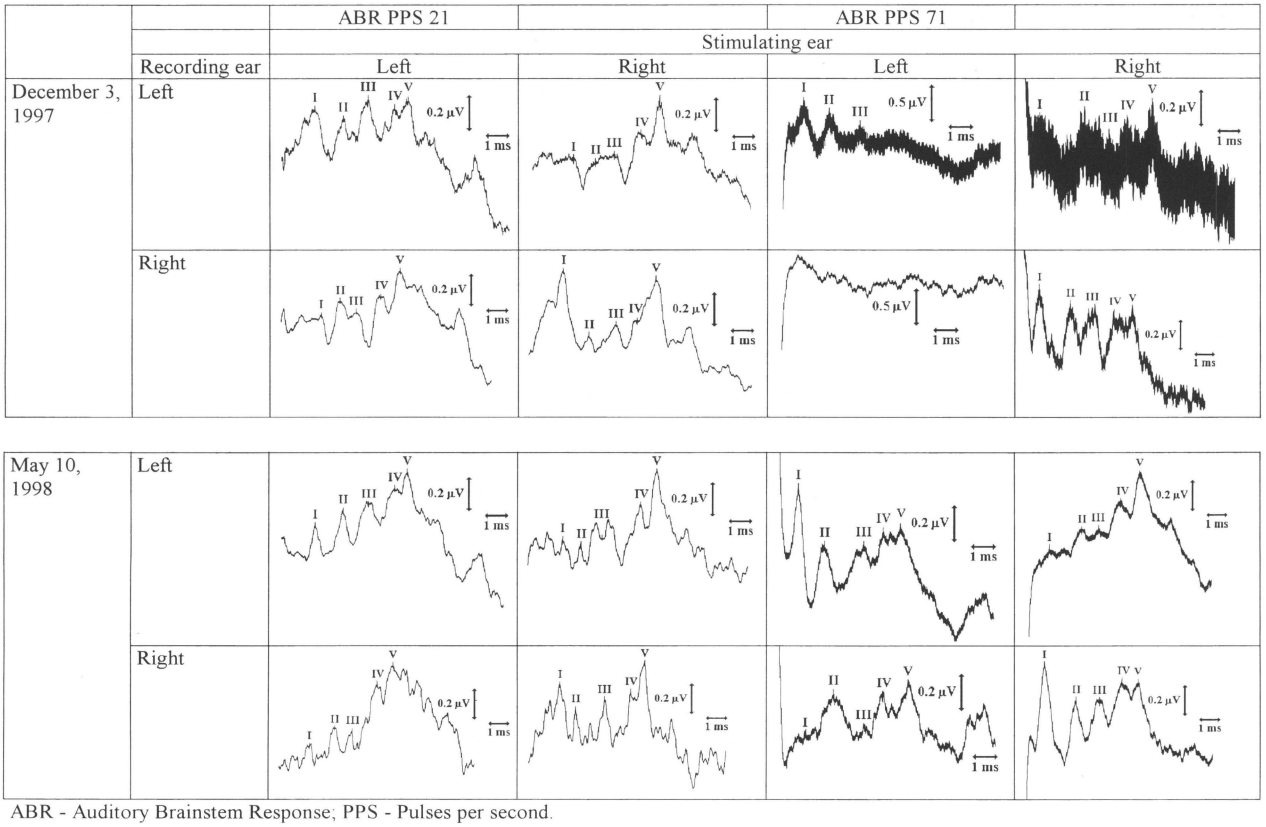
The averaged response waveform was marked automatically on each positive peak, and the positive peak latencies were measured and displayed in the measurement table. A manual correction of values was performed. The recording was stopped and was repeated in any case of obvious muscular activity or other artifact interference. The testing lasted, on average, 20 minutes.

### *Results of ABR and MLR Recordings*

ABR and MLR evaluations carried out on December 3, 1997 are presented in Figures 2 and 3. On habitual ABR sweep rate (PPS 21), the morphology of bilateral recordings was similar, with indication of smaller waves IV and V on the left-ear stimulation and ipsilateral register. No significant intraaural latency difference was seen (Table 1). Absolute latency values and interwave (IW) latency differences were within the limits of calibration values obtained from ten 20-year-old men with normal hearing.

At a higher sweep rate of ABR (PPS 71), a tetanic type of response was registered on the left-side recording, especially during right-ear stimulation (contralateral). During right-ear stimulation, especially on ipsilateral recording, a normal waveform pattern still was recognizable.

On left-ear stimulation, the ipsilateral (left) recording was irritable but normal until a very low wave III appeared. Later waves were annulled completely. No recognizable wave on the right-side recording (contralateral) was obtained.




ABR - Auditory Brainstem Response; PPS - Pulses per second.

**Figure 2.** The ABR recordings obtained on December 3, 1997, and May 10, 1998, on the patient HHCR, male, 19 years old. (ABR = auditory brainstem response; PPS = pulses per second.)

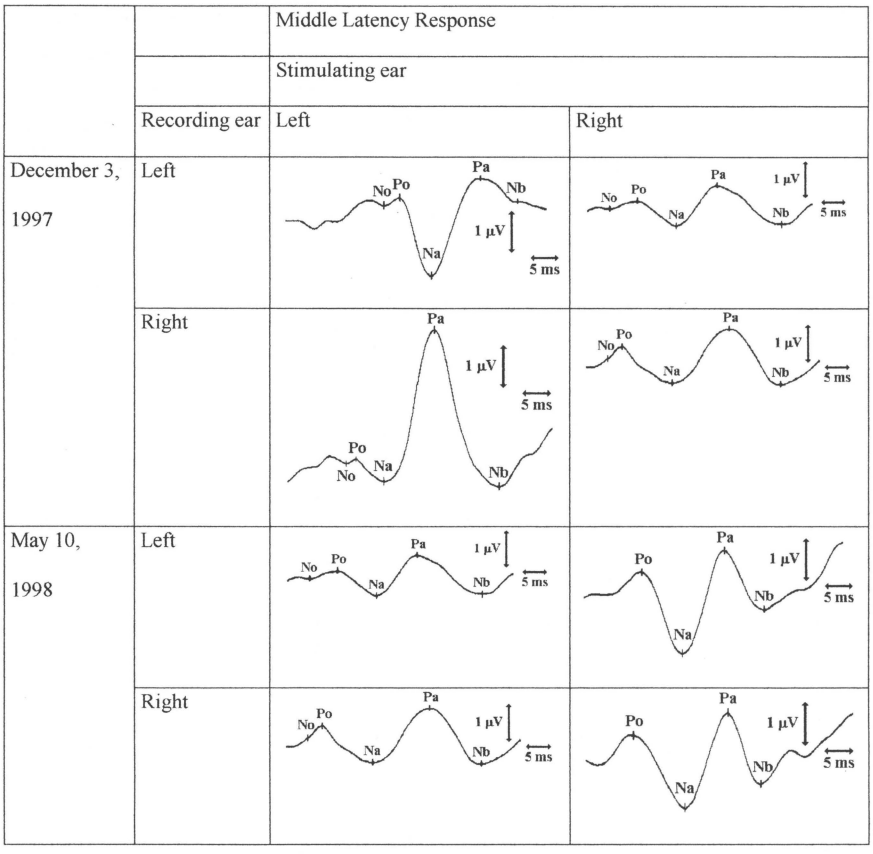



**Figure 3.** The middle latency response recordings obtained on December 3, 1997, and May 10, 1998 (patient HHCR, 19-year-old man).

Ipsilateral latencies on the left side were slightly shorter than were calibration values (see Table 1). A prolongation of the ipsilateral wave V latency was registered on the right side. All IW differences were prolonged on the right side.

MLR recordings on right-ear stimulation had normal morphology, even though without contralateral (left) facilitation (Fig. 3). MLR recordings were different during left-ear stimulation. At first sight, the response seemed more altered in right-side recording (contralateral). However, all latency values were within the calibration values (Table 2). The difference was the extremely high amplitude of the contralateral (right) Pa wave (see Fig. 3).

More altered was the ipsilateral (left) response on left-ear stimulation. The morphology was normal, but all ipsilateral latencies were prolonged (more than maximum of the calibration values; see Table 2).

On neural overload at the level of the higher mesencephalon, our results identified hyperexcitability, which was worse on the right side. A dysfunction with disappearance of waves representing higher levels (cranial-to-lateral lemniscus–inferior colicullus region) was registered on the left side. A dysfunction of principally thalamic (subcortical) temporal projections was identified on the left side. As the morphology was completely normal and only delayed, an ischemic lesion was suggested. Hyperexcitability at the subcortical level without morphological changes was registered on the right side.

### *Complementary Examinations*

Computed axial tomography and MRI indicated a small, isohypodense lesion located subcortically in the frontotemporal left region (Fig. 4). The image indicated an ischemic lesion.

Electroencephalography showed a θ rhythm in the left temporal region. Analytical blood testing (hematological, biochemical, and coagulation tests and tests for collagen vascular disease, autoimmunity, endocrine function, viral serology, syphilis, and the acquired immunodeficiency syndrome) were negative.

Cervical column radiography showed no alteration. Vertebral and carotid Doppler tests were normal. The patient did not give consent for cerebral angiography.

### *Medication*

The patient was medicated according to neuroprotective principles [1] with nimodipine, 30 mg 6/6 hours;

**Table 1.** Auditory Brainstem Response Ipsilateral Latency Values at Sweep Rates 21 and 71 on December 3, 1997, from Patient HHCR (male, 19 years old)

| | Right Ear | | | Left Ear | |
|---|---|---|---|---|---|
| **Wave** | **Latency (msec)** | **Calibration** | **I-A (msec)** | **Latency (msec)** | **Calibration** |
| ABR PPS 21 | | | | | |
| I | 1.53 | Median | 0.05 | 1.48 | $\bar{x}$ |
| II | 2.70 | +95% | 0 | 2.70 | Maximum |
| III | 3.89 | Maximum | 0.13 | 3.76 | Median |
| IV | 4.85 | $\bar{x}$ | 0.09 | 4.94 | +95% |
| V | 5.69 | +95% | 0.13 | 5.56 | Median |
| Interwave latency difference (msec) | | | | | |
| I–III | 2.36 | +95% maximum | 0.08 | 2.28 | $\bar{x}$ |
| III–V | 1.8 | Median | 0 | 1.8 | Median |
| I–V | 4.16 | +95% | 0.08 | 4.08 | $\bar{x}$ |
| ABR PPS 71 | | | | | |
| I | 1.39 | 0.06 msec < minimum | 0.12 | 1.51 | −95% |
| II | 2.99 | +95% | 0.36 | 2.63 | −95% |
| III | 4.14 | Median | 0.2 | 3.94 | Median |
| IV | 5.26 | $\bar{x}$ | — | — | — |
| V | 6.22 | 0.07 msec > maximum | — | — | — |
| Interwave latency difference (msec) | | | | | |
| I–III | 2.75 | 0.15 msec > maximum | 0.32 | 2.43 | +95% |
| III–V | 2.08 | Maximum | — | — | — |
| I–V | 4.83 | 0.12 msec > maximum | — | — | — |

ABR = auditory brainstem response; PPS = pulses per second; I-A = intraaural latency difference.
*Note:* Calibration signifies patient's ipsilateral latency values as compared to calibration results in ten 20-year-old men with normal hearing.

carbamazepine, 200 mg 12/12 hours; alprazolam, 0.5 mg 8/8 hours; vitamin B complex therapy (100 mg B1 + 200 mg $B_6$ + 200 mg $B_{12}$) 6/6 hours; and 127 mg of $Mg^{++}$ 12/12 hours.

## Second Observation

On May 10, 1998, the patient was declared well. He still had tinnitus, but it was changed in character and was no longer incapacitating. Tonal audiometry revealed tinnitus in the right ear, with the pure-tone characteristic, intensity of 15 dB HL (5 dB above the hearing threshold level), and frequency of 125 Hz (Fig. 5). Tympanometry, stapedial reflexes, and stapedial tone-decay tests were the same as on the first observation.

### *Results of ABR and MLR Recordings*

Results of ABR and MLR testing performed on May 10, 1998, are presented in Figures 2 and 3. ABR waveforms were symmetrical at 21 and 71 PPS. The morphology of the ipsilateral and contralateral response

**Table 2.** Middle Latency Response Values Recorded December 3, 1997, from Patient HHCR (a 19-year-old man)

| | | Middle Latency Response | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Po Wave | | Na Wave | | Pa Wave | | Nb Wave | |
| **Stimulating Ear** | **Recording Ear** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** |
| Right | Right | 7.85 | Minimum | 18.50 | +95% | 30.75 | +95% | 41.60 | +95% |
| — | Left | 10.95 | — | 19.60 | — | 28.65 | — | 43.15 | — |
| Left | Left | 21.80 | 7.75 msec > maximum | 27.9 | Maximum | 37.30 | 4.3 msec > maximum | 44.30 | Maximum |
| — | Right | 12.80 | — | 18.15 | — | 27.60 | — | 39.95 | — |
| I-A (msec) | Ipsilateral | 13.95 | — | 9.4 | — | 6.55 | — | 2.7 | — |
| — | Contralteral | 1.85 | — | 1.45 | — | 1.05 | — | 3.2 | — |

I-A = intraaural latency difference.
*Note*: Calibration signifies patient's ipsilateral latency values as compared to calibration results (n = ten 20-year-old men with normal hearing).

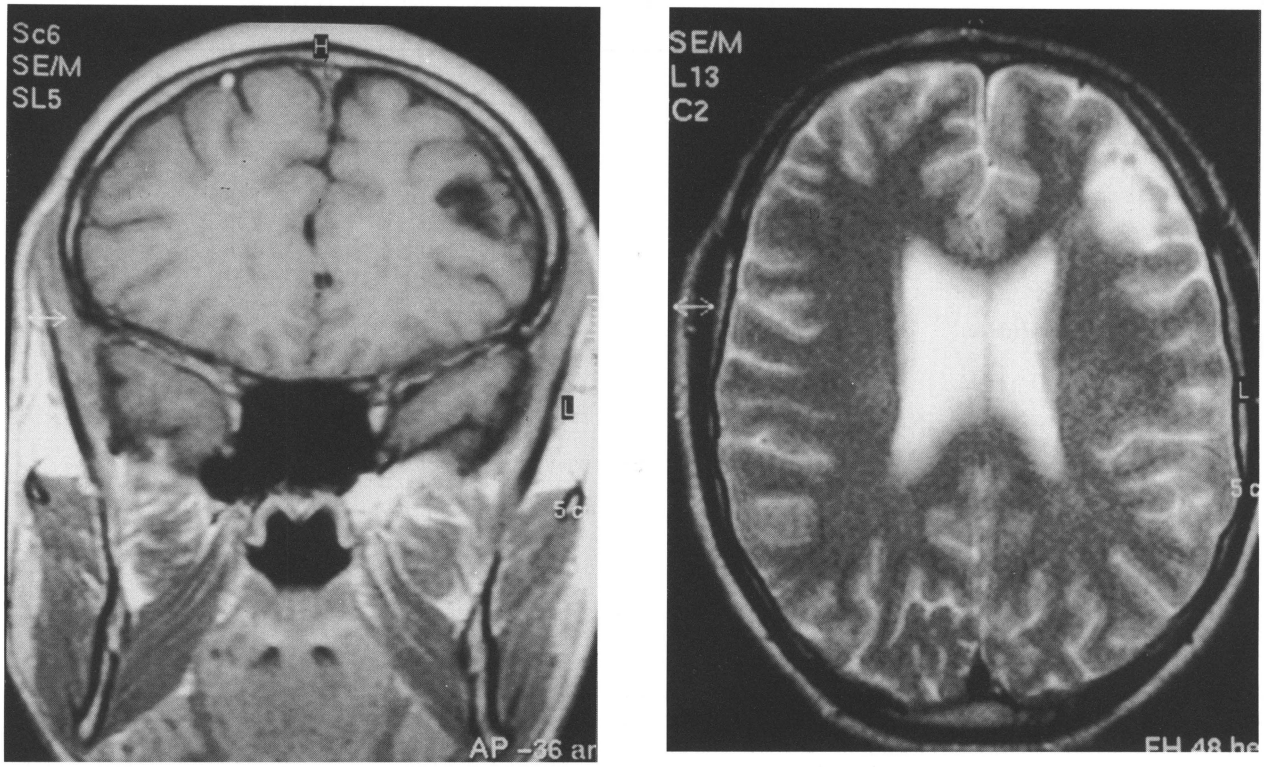



**Figure 4.** Magnetic resonance imaging of the brain on December 3, 1997 (patient HHCR, 19-year-old man).

was normal at PPS 21. At this sweep rate, intraaural latency differences were significant for all waves except wave III (Table 3). Probably this was the result of latency prolongation on the right side (more than the maximum of calibration values; see Table 3). The bilateral IW differences and latency values on the left side were within the limits of calibration.

The ipsilateral wave V amplitude was very low as compared to wave I at PPS 71 (see Fig. 2). The morphology of the ipsilateral and contralateral responses otherwise was normal but was better on the right recording side. All left ipsilateral latencies were within calibration values at PPS 71 (see Table 3). A latency prolongation of more cranial waves, representing the

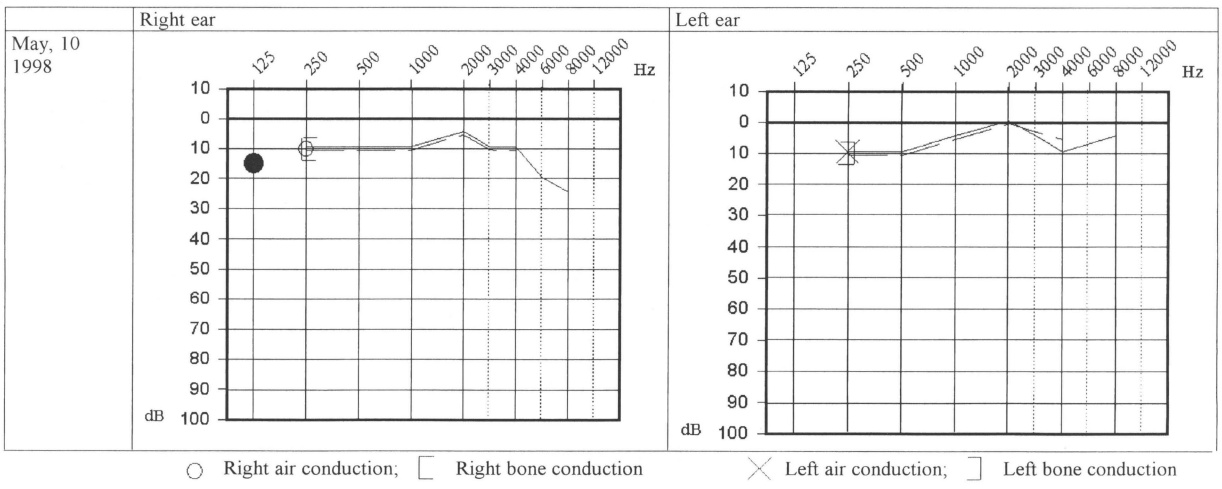



**Figure 5.** Hearing threshold level and tinnitus identification on May 10, 1998 (patient HHCR, 19-year-old man).

**Table 3.** Auditory Brainstem Response Ipsilateral Latency Values at Sweep Rates 21 and 71, Recorded May 10, 1998, from Patient HHCR (a 19-year-old man)

| | Right Ear | | | Left Ear | |
|---|---|---|---|---|---|
| **Wave** | **Latency (msec)** | **Calibration** | **I-A (msec)** | **Latency (msec)** | **Calibration** |
| ABR PPS 21 | | | | | |
| I | 1.64 | Maximum | 0.16 | 1.48 | $\bar{x}$ |
| II | 2.44 | 0.09 msec < minimum | 0.28 | 2.72 | Maximum |
| III | 3.91 | Maximum | 0.04 | 3.87 | +95% |
| IV | 5.22 | 0.1 msec > maximum | 0.19 | 5.03 | +95% |
| V | 5.92 | 0.07 msec > maximum | 0.32 | 5.6 | +95% |
| Interwave latency difference (msec) | | | | | |
| I–III | 2.27 | Median | 0.12 | 2.39 | +95% |
| III–V | 2.01 | +95% | 0.28 | 1.73 | Median |
| I–V | 4.28 | +95% | 0.16 | 4.12 | +95% |
| ABR PPS 71 | | | | | |
| I | 1.51 | −95% | 0.01 | 1.52 | −95% |
| II | 3.1 | +95% and between maximum | 0.46 | 2.64 | −95% |
| III | 4.28 | Maximum | 0.06 | 4.34 | +95% and between maximum |
| IV | 5.41 | +95% | 0.27 | 5.20 | $\bar{x}$ |
| V | 6.24 | 0.09 msec > maximum | 0.27 | 5.97 | Median |
| Interwave latency difference (msec) | | | | | |
| I–III | 2.77 | 0.17 > maximum | 0.05 | 2.82 | 0.18 msec > maximum |
| III–V | 1.96 | +95% | 0.33 | 1.63 | Minimum |
| I–V | 4.73 | Maximum | 0.28 | 4.45 | +95% and between maximum |

ABR = auditory brainstem response; PPS = pulses per second; I-A = intraaural latency difference.
*Note*: Calibration signifies patient's ipsilateral latency values as compared to calibration results (n = ten 20-year-old men with normal hearing.)

higher pons, was registered on the right side. IW differences indicated bilateral symmetrical prolongation at the lower pons and minimum calibration on the left superior pons.

MLR recordings were symmetrical and without significant difference in morphology (see Fig. 3). Amplitude and latency values of MLRs corresponded to calibration values (Table 4).

A change toward symmetry of waveforms was obvious in the second testing. At PPS 21, the main difference between the two tests was latency prolongation on the right side, although the results were within normal values. At PPS 71, no irritability was evident, and all waves were identifiable. MLR was symmetrical and normal bilaterally. Repeated MRI of the brain did not show any substantial difference as compared to the first MRI. (Fig. 6).

## DISCUSSION

The overlap of neurophysiological tests with the patient's subjective complaint and, finally, with morphological tests is obvious. We managed to identify the functional alteration, its qualitative type, and its location. From the results of neurophysiological testing, we

**Table 4.** Middle Latency Response Latency Values Recorded May 10, 1998, from patient HHCR (a 19-year-old man)

| | | Middle Latency Response | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Po Wave | | Na Wave | | Pa Wave | | Nb Wave | |
| **Stimulating Ear** | **Recording Ear** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** | **Latency (msec)** | **Calibration** |
| Right | Right | 8.90 | $\bar{x}$ | 18.45 | +95% | 26.45 | $\bar{x}$ | 32.55 | Median |
| — | Left | 11.10 | — | 18.90 | | 27.10 | | 34.85 | |
| Left | Left | 11.15 | +95% | 18.20 | Median | 25.90 | −95% | 32.60 | −95% |
| — | Right | 12.75 | — | 18.00 | — | 25.80 | — | 32.20 | — |
| I-A (msec) | Ipsilateral | 2.25 | — | 0.25 | — | 0.55 | — | 0.05 | — |
| — | Contralateral | 1.65 | — | 0.90 | — | 1.30 | | — | — |

I-A = intraaural latency differences.
*Note:* Calibration signifies patient's ipsilateral latency values as compared to calibration results (n = ten 20-year-old men with normal hearing).

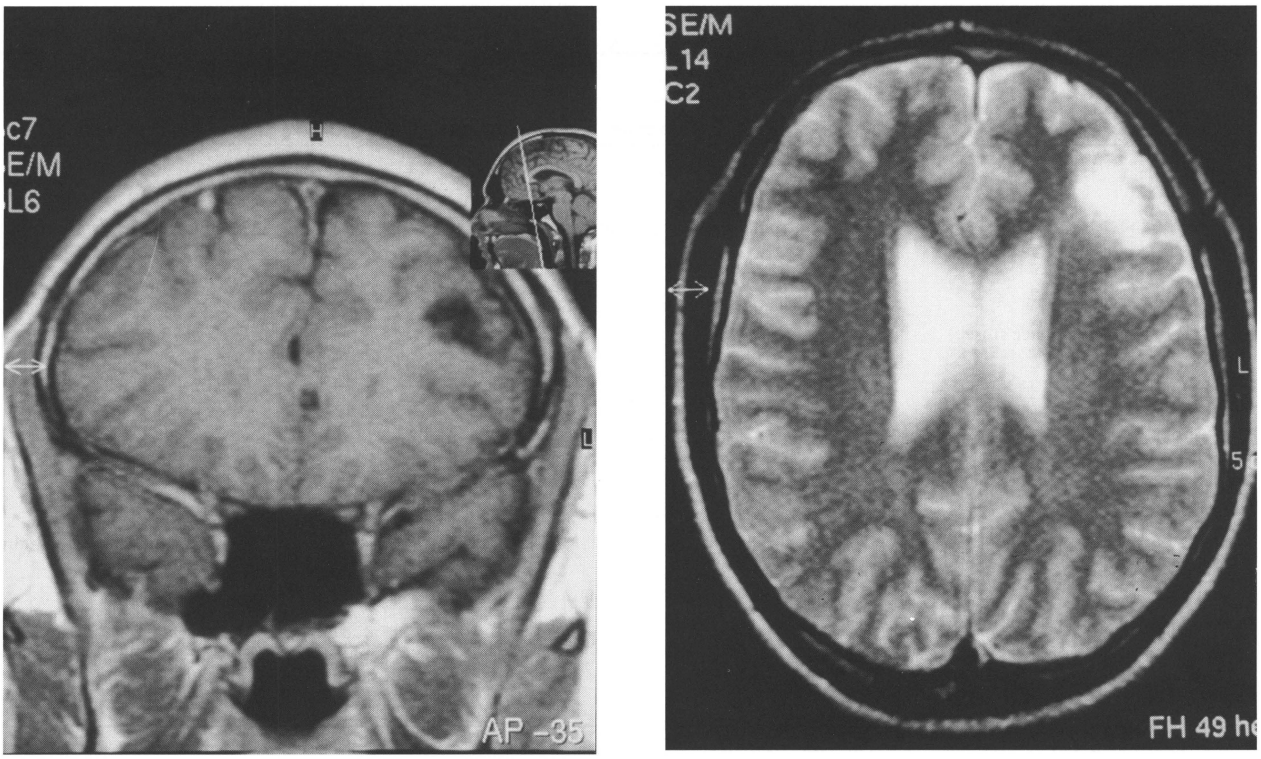



**Figure 6.** Magnetic resonance imaging of brain on May 10, 1998 (patient HHCR, 19-year-old man).

were able to determine and modify the medication regimen. We applied a functional method of follow-up, one that we believe is more sensitive than other methods generally applied and without nocive side effects.

In the first observation, on application of standard ABR parameters, we did not register any substantial difference. The utility of ABR is questioned, possibly owing to overexpectations or inadequate use of parameters [22]. The diagnosis in neurootology is made by a mosaic of little fragments, all of which are valuable and informative, and not on the basis of a single important test. Often, this fact is forgotten.

Moller et al. [29] did not find a significant difference of ABR in patients with tinnitus. However, all their patients had hearing loss (a steep-slope hearing loss on higher frequencies) [29,30], and the patients were manipulated intracranially [31]. Heffner's results [32] showed that perception is changed by intracranial manipulation. Such manipulation and the hearing loss change the neuronal activity and so render any conclusion difficult. Even so, hyperexcitability was indicated by the significant shortening of wave V latency [29]. Increasing the sweep rate of stimulation simulated a neural overload. A change in emphasis from the synchrony code at lower levels to a rate code at higher levels [33] renders a higher sweep rate more adequate for testing a higher mesencephalic region.

The amplitude alteration and the latency prolongation at a higher sweep rate are well-known. Recently, the evidence of a threshold for a neural reaction instigated the substitution of a linear progression model for latency prolongation [34]. This could be the reason for identification of dysfunction only on a sweep rate of PPS 71.

Our waveforms at PPS 71 demonstrated hyperexcitability similar to the recordings after tetanic stimulation of white matter in the auditory cortex of rats (particularly, supragranular pyramidal neurons activated principally by non-*N*-methyl-D-aspartate receptors) [35]. Contralateral recordings could be morphologically worse than ipsilateral because of horizontal spreading of supragranular field potential [35]. This could explain our left ABR waveform on contralateral stimulation. This effect could be the result also of predominant EI organization in higher auditory afferent structures [36].

The work of Kileny et al. [23] and, more recently, of McGee et al. [26] has described the alteration of MLR by subcortical and cortical lesions. No data were related to MLR and tinnitus in literature available to us.

El-Kashlan et al. [37] have obtained results similar to ours with MLR. They recorded MLR and autographic methods in guinea pigs to register central metabolic activity after prolonged deafferentation. No alteration occurred at the level of the ipsilateral or contralateral co-

chlear nucleus [37]. The area of superior olivary complex and LL showed ipsilateral reduction of activity and no contralateral alteration [37]. The area of IC in this case showed no reduction but with predominantly contralateral activity [37].

Left-ear stimulation registered an extremely high Pa-wave amplitude, indicating hyperactivity (perhaps compensatory) on the right side. This high amplitude could be a result of synchronized contributing neural activity [38], with an altered interactive process of adaptation [39].

The problem for us was identifying the cause of tinnitus in our patient, who exhibited evidence of hyperexcitability on the bilateral mesencephalic level, with dysfunction at higher left levels or delayed activity at the subcortical left side. Considering clinical characteristics of the complaint of our patient, the alteration should not be acute. The work of Irvine and Rajan [40] shows the absence of reorganization in acute lesions. In our case, the excitation as a result of suppression of lateral inhibition [40,41] indicated a certain chronic process. This plasticity might be one of the causes of tinnitus [42].

The location of alteration in our results could be seen as too wide and dispersed. Our lack of information about the functional specialization of multiple maps in the central auditory system is rendering localization difficult [43].

Despite the described alteration in function and identification of the lesion, the unique complaint of our patient was tinnitus. Nonetheless, function could be preserved even in complete ablations of auditory cortices [44]. This could be the result of the contribution of nonspecific auditory pathways or of partial preservation of AA structures [44,45].

The recuperation of our young patient after medical therapy was instituted was dramatic. This recovery might be attributable to functional reorganization within the central auditory pathway [46]. The organization could be based on preservation of rudimentary cochleotopic organization at the brainstem and auditory cortex [47], possibly in its immature state. Immature *N*-methyl-D-aspartate receptors are different from those in adults, needing greater electrical excitability that may serve as a trophic signal in a young person [11].

In our medical therapy, based on neuroprotection [1] and the facts mentioned, we intended only to orient the neural activity of our patient, avoiding oversedation [11]. Probable sedative effect was visible in latency prolongation on the right side during the second observation. The goal was to diminish excitotoxicity and to apply antioxidant therapy. As the alteration was not acute, we did not apply corticosteroids. Special attention should be given to the quantity of a specific drug. Different qualitative properties might be provoked with different quantities of the same drug [48,49].

## SUMMARY

The qualitative objectivization of tinnitus is the foundation on which tinnitus medical therapy is based. ABR and MLR could be used in diagnosis and functional follow-up of tinnitus patients. A higher sweep rate of stimulation could be a more sensitive method for a subtle dysfunction screening.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of Professor Manuel Pais Clemente, head of the department of otorhinolaryngology, Hospital São João, Medical School, Porto, Portugal. The authors are grateful to Aurelina Ribeiro and Alcina Falção for carrying out technical routine work. We also thank Maria João Martins for technical advice.

## REFERENCES

1. Shulman A. Neuroprotective drug therapy: A medical and pharmacological treatment for tinnitus control. *Int Tinnitus J* 3(2):77–93, 1997.
2. Stracher A. Caplain inhibitors as neuroprotective agents in neurodegenerative disorders. *Int Tinnitus J* 3(2):71–75, 1997.
3. Denk DM, Heinzl H, Franz P, Ehrenberger K. Cavoverine in tinnitus treatment. A placebo-controlled blind study. *Acta Otolaryngol (Stockh)* 117:825–830, 1997.
4. Reser DH, van de Water TR. Implications of neurotrophin supported auditory neuron survival for maintenance of the tonotopic organization of the central auditory pathway. *Acta Otolaryngol (Stockh)* 117: 239–243, 1997.
5. Shiomi Y, Nagamine T, Fujiki N, et al. Tinnitus remission by lidocaine demonstrated by auditory-evoked magnetoencephalogram. *Acta Otolaryngol (Stockh)* 117:31–34, 1997.
6. Rahko T, Kotti V. Tinnitus treatment by transcutaneous nerve stimulation (TNS). *Acta Otolaryngol Suppl (Stockh)* 529:88–89, 1997.
7. Matushima JI, Kumagai M, Takeichi N, et al. Improved word perception in tinnitus patients following electrical stimulation of the ear: A preliminary report. *Acta Otolaryngol Suppl (Stockh)* 532:115–118, 1997.
8. Matsushima JI, Kumagai M, Kamada T, et al. Preliminary study of improved perception of words with the same sound but different intonation in tinnitus patients following electrical stimulation of the ear. *Acta Otolaryngol Suppl (Stockh)* 532:112–114, 1997.
9. Okada M, Ishihara K, Sasa M, et al. Enhancement of GABA-mediated inhibition of rat medial vestibular nu-

cleus neurons by the neurosteroid 20-hydroxyecdysone. *Acta Otolaryngol (Stockh)* 118:11–16, 1998.

10. Goldstein B. A call for standards and outcome measures for tinnitus diagnosis/treatment. *Int Tinnitus J* 3(2):69–70, 1997.
11. Puel JL, d'Aldin C, Ruel J, et al. Synaptic repair mechanism responsible for functional recovery in various cochlear pathologies. *Acta Otolaryngol (Stockh)* 117:214–218, 1997.
12. Tennigkeit F, Puil E, Schwarz DWF. Firing modes and membrane properties in lemniscal auditory thalamus. *Acta Otolaryngol (Stockh)* 117:254–257, 1997.
13. Kimitsuki T, Nakagawa T, Hisashi K, et al. Elevation of intracellular calcium induced by the intrapipette perfusion technique modifies membrane ion currents in the chick cochlear hair cell. *Acta Otolaryngol (Stockh)* 118:70–73, 1998.
14. Nario K, Kitano I, Mori N, Matsunaga T. Effect of endoplasmic $Ca^2$+-ATPase inhibitors on cochlear potentials in the guinea-pig. *Acta Otolaryngol (Stockh)* 118:198–205, 1998.
15. Nishizaki K, Anniko M, Orita Y, et al. Programmed cell death in the developing epithelium of the mouse inner ear. *Acta Otolaryngol (Stockh)* 118:96–100, 1998.
16. Versnel H, Mossop JE, Moore DR. Optical imaging of intrinsic signals in ferret auditory cortex. *Br J Audiol* 32(2):93, 1998.
17. Hall DA, Akeroyd MA, Palmer AR, et al. Measuring haemodynamic changes in auditory cortex using functional Magnetic Resonance Imaging (fMRI). *Br J Audiol* 32(2):95–96,1998.
18. Imaizumi S, Mori K, Kiritani S, Yumoto M. Observation of neural processes of auditory scene analysis by magnetoencephalography. *Acta Otolaryngol Suppl (Stockh)* 532:106–108, 1997.
19. Ohnishi M, Kusakawa N, Masaki S, et al. Measurement of hemodynamics of auditory cortex using magnetoencephalography and near infrared spectroscopy. *Acta Otolaryngol Suppl (Stockh)* 532:129–131, 1997.
20. Denk DM, Brix R, Felix D, Ehrenberger K. Tinnitus Therapy with Transmitters. In JM Aran, R Dauman (eds), Tinnitus 91. Amsterdam: Kugler, 1992:119–121.
21. Shulman A. A final common pathway for tinnitus in the medial temporal lobe system. *Int Tinnitus J* 1:115–126, 1995.
22. Kotlarz JP, Eby TL, Borton TE. Analysis of the efficiency of retrocochlear screening. *Laryngoscope* 102:1108–1112, 1992.
23. Kileny P, Paccioretti D, Wilson AT. Effects of cortical lesions on middle latency response (MLR). *Electroenceph Clin Neurophysiol* 66:108–120, 1987.
24. Littman T, Kraus N, McGee T, Nicol T. Binaural stimulation reveals functional differences between midline and temporal components of middle latency response in guinea pigs. *Electroenceph Clin Neurophysiol* 84:362–372, 1992.
25. Buchwald JS, Rubinstein EH, Schwafel J, Strandburg RJ. Midlatency auditory evoked responses: Differential effects of a cholinergic agonist and antagonist. *Electroenceph Clin Neurophysiol* 80:303–309, 1991.
26. McGee T, Kraus N, Comperatore C, Nicol T. Sucortical and cortical components of the MLR generating system. *Brain Res* 544:211–220, 1991.
27. Raeva S, Lukashev A. Unit activity in human thalamic reticularis neurons: II. Activity evoked by significant and nonsignificant verbal or sensory stimuli. *Electroenceph Clin Neurophysiol* 86:110–122, 1993.
28. Jastreboff PJ, Hazell JWP. A neurophysiological approach to tinnitus: Clinical implications. *Br J Audiol* 27: 7–17, 1993.
29. Moller AR, Moller MB, Jannetta PJ, Jho HD. Compound action potentials recorded from the exposed eight nerve in patients with intractable tinnitus. *Laryngoscope* 102: 187–197, 1992.
30. Moller AR, Moller MB, Yokota M. Some forms of tinnitus may involve the extralemniscal auditory pathway. *Laryngoscope* 102:1165–1171, 1992.
31. Moller MB, Moller AR, Jannetta PJ, Jho HD. Vascular decompression surgery for severe tinnitus: Selection criteria and results. *Laryngoscope* 103:421–427, 1993.
32. Heffner HE. The role of macaque auditory cortex in sound localization. *Acta Otolaryngol Suppl (Stockh)* 532:22–27, 1997.
33. Schulze H, Langer G. Representation of periodicity pitch in the primary auditory cortex of the mongolian gerbil. *Acta Otolaryngol Suppl (Stockh)* 532:89–95, 1997.
34. Heil P. Aspects of temporal processing of FM stimuli in primary auditory cortex. *Acta Otolaryngol Suppl (Stockh)* 532:99–102, 1997.
35. Kudoh M, Shibuki K. Comparison of long-term potentials between the auditory and visual cortices. *Acta Otolaryngol Suppl (Stockh)* 532:109–111, 1997.
36. Jen PHS, Sun X, Shen JX, et al. Cytoarchitecture and sound activated responses in the auditory cortex of the big brown bat, *Epitesicus fuscus. Acta Otolaryngol Suppl (Stockh)* 532:61–67, 1997.
37. El-Kashlan HK, Noorily AD, Nirpako JK, Miller JM. Metabolic activity of the central auditory structures following prolonged deafferentation. *Laryngoscope* 103: 399–405, 1993.
38. Brown M, McAnally KI, Clark GM. Variability of amplitude and area of the auditory nerve compound action potential. *Acta Otolaryngol (Stockh)* 117:836–840, 1997.
39. Finlayson PG, Adam TJ. Short-term adaptation of excitation and inhibition shapes binaural processing. *Acta Otolaryngol (Stockh)* 117:187–191, 1997.
40. Irvine DRF, Rajan R. Injury-induced reorganization of frequency maps in adult auditory cortex: The role of unmasking of normally-inhibited inputs. *Acta Otolaryngol Suppl (Stockh)* 532:39–45, 1997.
41. Suga N. Tribute to Ysasuji Katsuki's major findings: Sharpening of frequency tuning in the central auditory system. *Acta Otolaryngol Suppl (Stockh)* 532:9–12, 1997.
42. Naito Y, Hirano S, Honjo I, et al. Sound-induced activation of auditory cortices in cochlear implant users with post- and prelingual deafness demonstrated by positron

emission tomography. *Acta Otolaryngol (Stockh)* 117: 490–496, 1997.

43. Rauschecker JP. Processing of complex sounds in the auditory cortex of cat, monkey, and man. *Acta Otolaryngol Suppl (Stockh)* 532:34–38, 1997.
44. Kaga K, Shindo M, Tanaka Y. Central auditory information processing in patients with bilateral auditory cortex lesions. *Acta Otolaryngol Suppl (Stockh)* 532:77–82, 1997.
45. Ojima H, He J-F. Cortical convergence originating from domains representing different frequencies in the cat AI. *Acta Otolaryngol Suppl (Stockh)* 532:126–128, 1997.
46. Shepherd RK, Hartmann R, Heid S, et al. The cental auditory system and auditory deprivation: Experience with cochlear implants in the congenitally deaf. *Acta Otolaryngol Suppl (Stockh)* 532:28–33, 1997.
47. Eggermont JJ, Ponton CW, Don M, et al. Maturational delays in cortical evoked potentials in cochlear implant user. *Acta Otolaryngol (Stockh)* 117:161–163, 1997.
48. Laurikainen E, Hussain S, Miller JM, Nuttall AL. Nonspecific effect of bettahistine on cochlear electrophysiology in guinea pig. *Acta Otolaryngol Suppl (Stockh)* 532:77–79, 1997.
49. Jager W, Brundin L, Idrizbegocic E, Flock A. Effects of local anaesthetics on the gross receptor potentials in the guinea pig cochlea. *Acta Otolaryngol (Stockh)* 117: 49–54,1997.