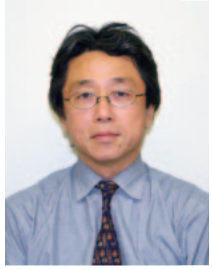
Evoked Potentials in Response to Electrical Stimulation of the Cochlear Nucleus by Means a Multi-channel Surface Microelectrode



Kiyoshi Oda[2)], Tetsuaki Kawase*[1)], Daisuke Yamauchi, Yukio Katori, and Toshimitsu Kobayashi

* Professor
1) Laboratory of Rehabilitative Auditory Science, Graduate School of Biomedical Engineering
2) Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine
E-mail: oda@orl.med.tohoku.ac.jp, kaw@m.tains.tohoku.ac.jp

1. Introduction

Auditory brainstem implants (ABI) are an artificial organ technology in which electrodes are implanted in the brainstem in order to restore the hearing of patients who have lost their hearing as a result of auditory nerve dysfunction. Cochlear implants, which bypass the inner ear and provide information to the hearing centers through direct stimulation of the auditory nerve, have already come into wide clinical use in Japan. In contrast, ABI attempt to restore auditory function by directly stimulating the cochlear nucleus in the auditory brainstem.

Auditory brainstem implants are primarily indicated in the case of neurofibromatosis type II, a hereditary autosomal dominant disorder which typically presents as bilateral acoustic neurofibromatosis. This disorder is recognized by the Japanese Ministry of Health, Labor and Welfare as a specified disease whose treatment qualifies for special government subsidies (incidence: 1/35,000). Patients with this disorder typically lose their hearing sooner or later as the tumor increases in size, and until now no effective treatment has been available for patients once they have lost their auditory function. As a result, patients suffering from this disorder are subject to a great deal of misery and anxiety.

In recent years the clinical application of cochlear implants has been very effective in restoring the hearing of patients with cochlear hearing loss, but they are not effective in the case of diseases such as the one described above which are the result of auditory nerve dysfunction. Because this is a hereditary disease, a gene therapy should theoretically provide a fundamental cure, but the likelihood of an effective gene therapy being developed in the foreseeable future is extremely low, so other clinical modalities for restoring auditory function in these patients are urgently required.

Auditory brainstem implants have reached the clinical trial stage in Europe and the United States [1-3]. Satisfactory outcomes have been demonstrated in successful cases; however, the success rate has been less than satisfactory [1-3], and various problems need to be solved as quickly as possible so that these devices can be put to effective clinical use in Japan.

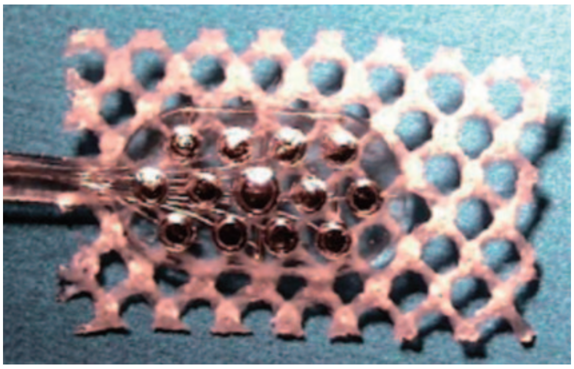


Fig. 1. Electrode of an auditory brainstem implant (MED-EL^{R} Surface electrode)
Dimensions: 5.5 mm X 3 mm; number of electrodes: 12. The device is placed on the surface of the auditory brainstem, on top of the cochlear nucleus.

The reasons that ABI, which also use electrical impulses to medically restore auditory function, have a poorer record of success than cochlear implants may be summarized as follows.

1. ABI stimulate the cochlear nucleus by means of a surface electrode (Fig. 1), but because of side effects, the actual number of electrodes that can be used is limited.
2. The tonotopic organization of the cochlear nucleus is considerably more complex than that of the cochlea, and high-precision frequency mapping is difficult.
3. In the case of cochlear implants, electrodes are inserted into the scala tympani; in ABI, however, it is often impossible to identify the optimal site for electrode implantation on the basis of anatomical criteria alone. As a result, inter-operative electrophysiological mapping is generally used to determine the implant site [4]. However, the devices presently in clinical use feature inter-electrode distances of several mm or more (Fig. 2), so the level of precision is inadequate.

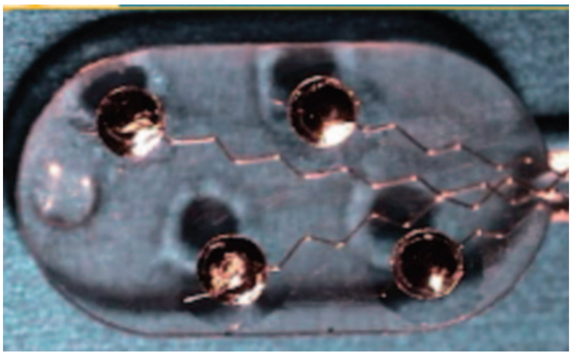


Fig. 2. Probe used clinically to determine implant site (MED-EL[R])
In actual ABI surgery, two of the four electrodes on the probe are stimulated randomly and the auditory brainstem response is recorded. The probe is 5 mm long and 3 mm wide

Attention has been focused on trying to improve the results of ABI by using needle electrodes to stimulate deeper portions of the brainstem, but for this method to be successful, it will be necessary to map the cochlear nucleus with greater accuracy.

In the present study a multi-channel surface microelectrode was employed to measure electrical evoked auditory responses, and these responses were utilized to map the cochlear nucleus in an animal model.

2. Results of Our Research Through 2007

Last year (2007) we carried out electrophysiological mapping of the cochlear nucleus in guinea pigs using the 64-channel microelectrode (MED64) shown in Fig. 3 (left) to measure the electrical evoked auditory responses. We obtained the following results.

- Evoked auditory brainstem response (EABR) waveforms were generated by 100-µA bipolar stimulation with excellent reproducibility.
- In nearly all cases, the boundary between stimulation points that generated EABR waveforms and those that failed to generate EABR waveforms could be clearly distinguished (when the 100-µm stimulation points were shifted to the borderline region, EABR waveforms were no longer recorded).
- Results are sometimes affected by surface conditions where the electrical stimulation is applied, and this must be taken into account when interpreting the results.

The above findings demonstrated the feasibility of using microelectrodes for electrophysiological mapping, so during the current year we 1) carried out electrophysiological mapping using a larger 260-channel microelectrode system (Fig. 3, right), and 2) we also tested a single channel microelectrode system (bipolar), coupled with a navigation system designed to allow for on-screen virtual mapping.

3. Electrophysiological Mapping Using a 260-Channel Microelectrode System

3.1. Methods

The animals used were guinea pigs weighing 500 g. After intramuscular anesthetization with ketamine (60 mg/kg) and xylazine (5 mg/kg), a click stimulus was

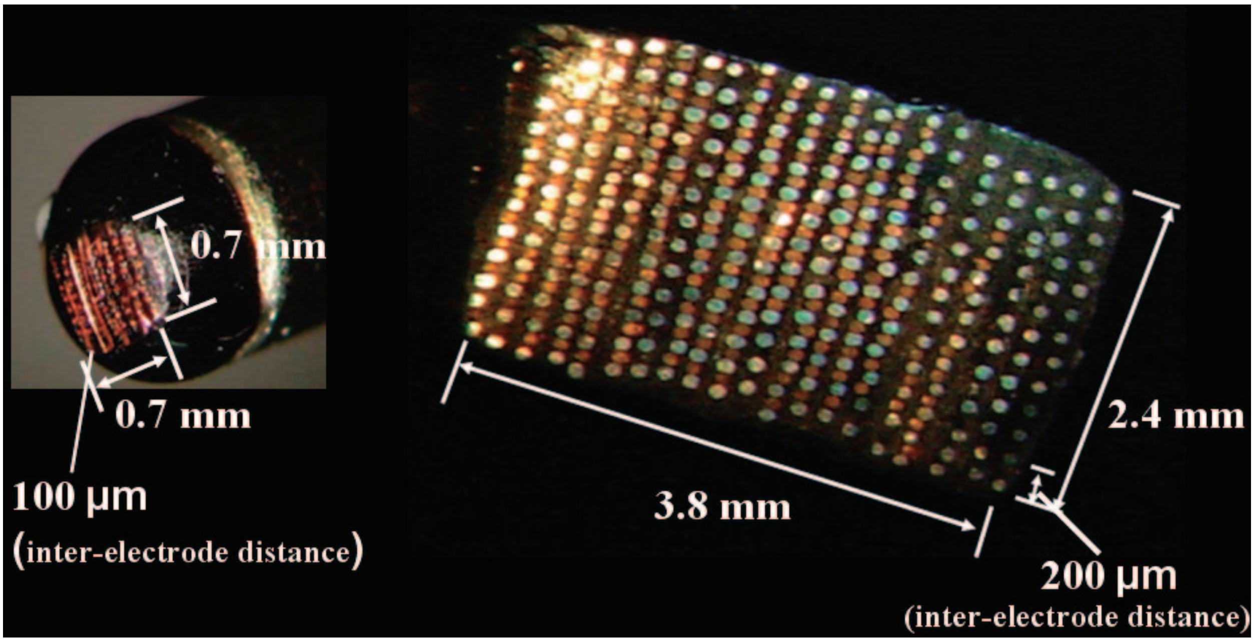


Fig. 3. 64-channel microelectrode (left), and 260-channel microelectrode (right).
64-channel size: 0.7 mm x 0.7 mm; inter-electrode distance: 100µm; number of electrodes: 64; electrode diameter: 50µm

used to measure the auditory evoked brainstem response (AABR) (Neuropack μ, Nihon Kohden) in order to confirm normal auditory function.

The animals were then placed in a supine position, and an incision was made in the skin behind the ear to expose and remove the skull to allow cerebellar retraction and subsequent visualization of the cochlear nucleus. The 260-channel microelectrode shown in Fig. 3 was then placed on the surface of the cochlear nucleus. This device has 260 electrodes in an area of 3.8 mm x 2.4 mm, with an inter-electrode distance of 200 μm.

Of the 260 electrode channels on this microelectrode, two points were stimulated arbitrarily and the electrical evoked brainstem responses (EABR) were recorded. In order to record the EABR, the active electrodes were placed on the surface of the auditory region, the reference electrodes, consisting of stainless steel needles, were placed behind the ear, and the ground was located in the frontal region. EABR were recorded using the same system as for the auditory brainstem responses (AABR) (Neuropack μ, Nihon-Kohden) under the following measurement conditions: number of averages, 100; low-cut filter, 200-1000 Hz; high-cut filter, 3000 Hz.

As regards the electrical stimuli, a SEN-3041 pulse generator (Nihon Kohden) and SS-203J Isolator were used to generate bipolar pulses of 80-μsec duration.

3.2. Results

1) EABR waveform recording system

Using the prototype 64-channel system with 100-μA bipolar stimulation, we succeeded in recording reproducible EABR when the cochlear nucleus was stimulated electrically.

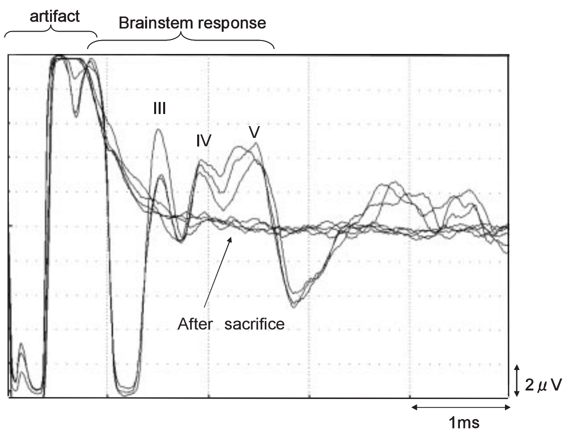


Fig. 4. Representative EABR waveforms.
Following the artifact generated by the electrical stimulation process, waveforms were recorded which were considered equivalent to waves III, IV, and V seen in auditory evoked brainstem responses. These latter waveforms disappeared after the animals were sacrificed, clearly confirming that they were not electrical artifacts.

Representative EABR waveforms after typical electrical stimulation of the cochlear nucleus are shown in Fig. 4.

In the case of acoustically evoked responses (AABR), 5-6 wave peaks are recorded from the spiral ganglion to the colliculus inferior [5], but in AABR generated by electrical stimulation of the cochlear nucleus, the peaks show individual variability. In humans, 1-4 peaks have been reported [1].

There are various theories about the origin of these waveforms; however, it is considered that wave I is related to the ipsilateral cochlear nerves, wave II is related to the ipsilateral cochlear nucleus, and wave III is related to the contralateral superior olive nucleus [2]. In EABR, wave II is obscured by an artifact generated by the electrical stimulation, therefore the auditory brainstem response to electrical stimulation of the cochlear nucleus is thought to appear after wave III (Fig. 5). In the example shown here, waveforms thought to correspond to waves III through V are observed following the electrical artifact.

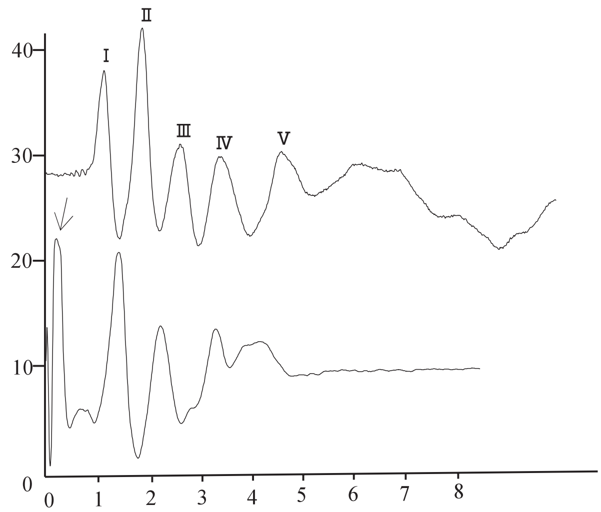


Fig. 5. ABR and EABR
The level of stimulation current (μV) is shown on the vertical axis, with time (ms) indicated on the horizontal axis. The ABR at the top is after a 90-dB click stimulus, while that at the bottom was obtained after electrical stimulation. The arrow indicates an artifact caused by the electrical stimulation

These latter waveforms disappeared after the animals were sacrificed, confirming that they were not electrical artifacts.

2) Input/output characteristics

Figure 6 shows the input/output characteristics obtained from the 260-channel microelectrode placed on the surface of the cochlear nucleus. The threshold value was 50 μA, and saturation started to appear at around 1000 μA. Shown here is a representative case; however, nearly all cases presented a similar profile.

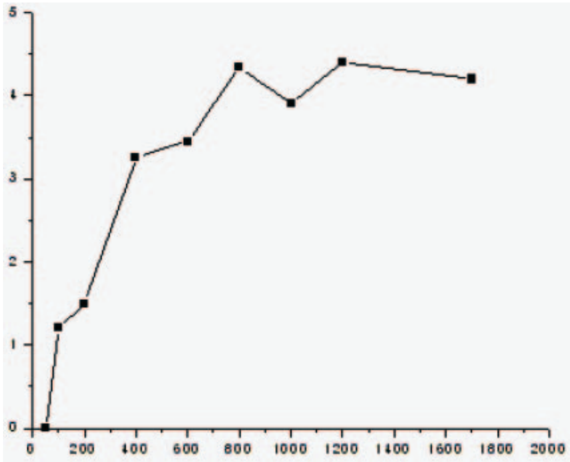


Fig. 6. Input/output characteristics
Wave III amplitude (mV) is shown on the vertical axis, while the level of stimulation current (μA) is shown on the horizontal axis. The threshold value was 50μA; saturation was gradually observed at levels above 1000μA.

3.3. Electrophysiological mapping of the cochlear nucleus using the 260-channel microelectrode system

Next we attempted to use this system to perform electrophysiological mapping of the cochlear nucleus. Mapping is considered to be most effective when the stimulation used is capable of recording reproducible waveforms with high sensitivity and an excellent S/N.

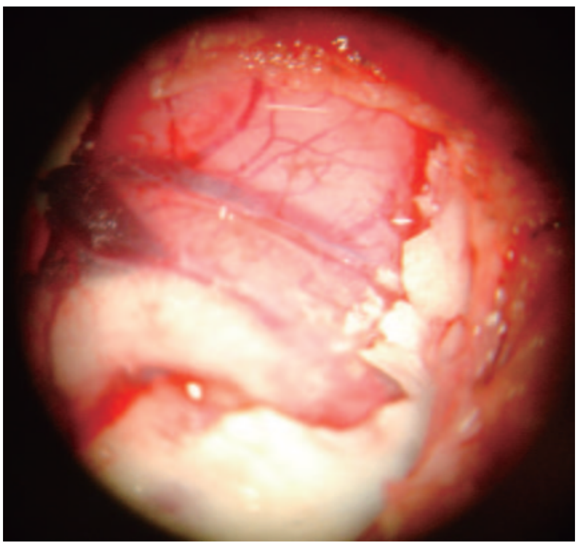


Fig. 7. Right cochlear nucleus
Operative field in the animal experiment. The cochlea is destroyed and the cerebellum displaced to reveal the cochlear nucleus. Dashed lines indicate the boundaries of the area upon which the 260-channel microelectrode was placed.

Therefore, after taking into consideration the I/O characteristics of the EABR shown in Fig. 5, electrical stimulation from the dynamic portion of the signal (400 μA -800 μA) was used to carry out the mapping.

Figure 7 shows the operative field with the 260-channel microelectrode placed on the surface of the cochlear nucleus.

The temporal bulla of the guinea pig was largely removed and the cerebellum displaced to expose the cochlear nucleus. As shown in Fig. 7, the 260-channel microelectrode was placed so as to straddle the upper border of the cochlear nucleus.

We describe below two cases in which the cochlear nucleus was mapped using the 260-channel microelectrode.

In the first case (Fig. 8), 200-μm bipolar stimulation was carried out at 63 locations. Negative results were obtained at 22 of these locations, while positive results were observed at the remaining 41 locations. The border between the two areas was clearly delineated. This is thought to represent the boundary between the dorsal side of the cochlear nucleus and the cerebellum.

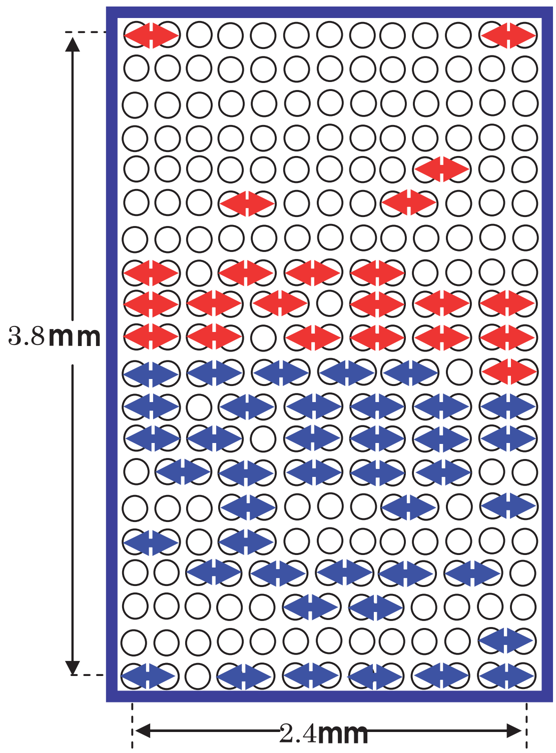


Fig. 8. Electrophysiological mapping of the cochlear nucleus using the 260-channel microelectrode. (Case 1) Dorsal side is at the top, and the mouth is to the right. Red arrows indicate positions where EABR were detected (22 locations); green arrows indicate positions where no EABR were detected (41 locations).

In the second case (Fig. 9), 200-μm bipolar stimulation was carried out at 70 locations, 1166-μm bipolar stimulation was carried out at 4 locations, and 4494-μm bipolar stimulation was carried out at 2 locations. In the case of 200-μm bipolar stimulation, 21 locations produced negative results, whereas 49 locations produced positive results. The border between the two areas was clearly delineated, and was considered to represent the boundary between the dorsal side of the cochlear nucleus and the cerebellum. In the case of 4494-μm bipolar stimulation, where the gap between electrodes was largest, the stimulation points included both positive and negative areas as defined by the 200-μm bipolar stimulation. A positive EABR waveform was observed.

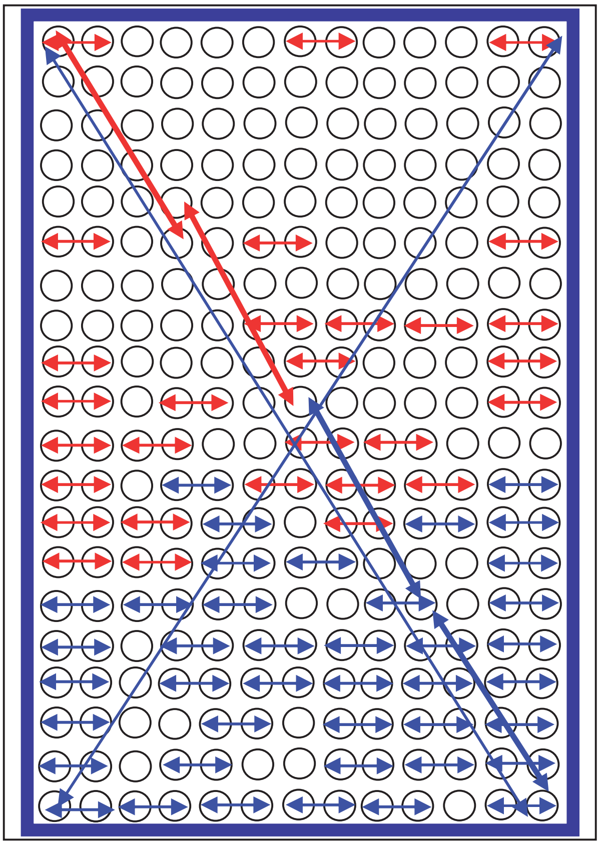


Fig. 9. Electrophysiological mapping of the cochlear nucleus using the 260-channel microelectrode. (Case 2) Dorsal side is at the top, and the mouth is to the right. The electrode gap was 200 μm (70 locations), 1166 μm (4 locations) or 4494 μm (2 locations). Red arrows indicate positions where EABR were detected (31 locations); green arrows indicate positions where no EABR were detected (45 locations).

This may also prove, moreover, that the four corners of the 260-channel microelectrode were in direct contact with the brain.

Results for the four locations subjected to 1166-μm bipolar stimulation were, counting from the dorsal side, negative, negative, positive, positive, in that order. Compared with the results from the 200-μm bipolar stimulation, these four points (shown in parentheses) connected regions that were negative (negative), negative (negative), negative (positive), and positive (positive), in that order.

3.4. Summary

These results demonstrated that selective stimulation and electrophysiological mapping of the cochlear nucleus were feasible even when using a stimulating electrode with an interelectrode distance as large as 200 μm. Moreover, as shown in Fig. 9, three different interelectrode distances were used in the two cases described above: 200 μm, 1166 μm, and 4494 μm. When the interelectrode distance is relatively large, our findings indicate that if one electrode is in the positive response zone and the other is in the negative response zone, the bipolar stimulation is likely to generate a positive response. This result supports the theory that the results of electrophysiological mapping should improve as the distance between electrodes becomes smaller and as the number of stimulation points increases. Further study will be necessary to clarify the relationship between the anatomical boundaries and those delineated by the electrophysiological mapping, however it is clear that bipolar stimulation using interelectrode distances of 100-200 μm is capable of producing clear EABR. Furthermore, following very slight shifts in the stimulation region, the EABR suddenly disappeared or the shape of the waveforms changed, indicating that the microelectrode used was capable of applying relatively localized electrical stimulation. These results indicate that the use of a microelectrode as the stimulating electrode in ABI may make it possible to achieve a more precise discrimination of pitch.

The main purpose of the present study was to evaluate the usefulness of this multi-channel surface microelectrode in mapping the cochlear nucleus, so the EABRs in response to the electrical stimulation of the cochlear nucleus were evaluated. In the future, by measuring the frequency response in the auditory cortex after electrical stimulation of the cochlear nucleus, it should be possible to specifically examine frequency discrimination of the narrow bipolar stimulation.

4. Study of a Virtual Mapping System Consisting of a Single Channel Microelectrode System (Bipolar) Coupled with a Navigation System

4.1. Method

1) Stimulating electrode

The prototype of this electrode stimulation system is illustrated in Figs. 10 and 11. It consists of a single channel bipolar electrode with a 100-mm long handle and 100m shaft. An antenna for 3D navigation can be attached to the handle section.

Fig. 10. Prototype microelectrode for human use
Overall length of handle is 100 mm; the shaft section is also 100 mm. It uses a flat single channel bipolar electrode. An antenna for the 3D navigation system can be attached to the handle section. (*)

EABR were recorded using the same system as for AABR (Neuropack μ, Nihon-Kohden) under the following measurement conditions: number of averages, 3000; low-cut filter, 200 Hz; high-cut filter, 3000 Hz.

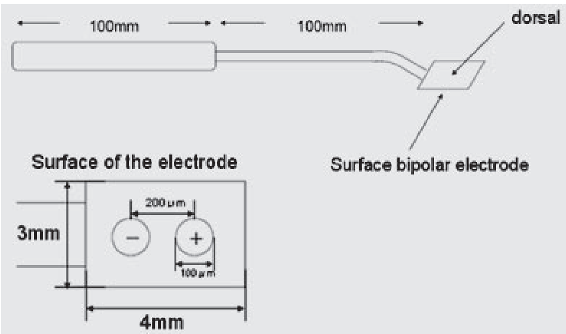


Fig. 11. Prototype specifications
Overall handle length: 100 mm; shaft length: 100 mm; electrode: single channel bipolar flat electrode; interelectrode distance: 200 μm; electrode diameter: 100 μm.

As regards the electrical stimuli, a SEN-3041 pulse generator (Nihon Kohden) and SS-203J Isolator were used to generate 80-μsec bipolar pulses. Stimulation frequency was 20 Hz, and stimulation voltage was 500 or 1000 μA.

2) Mapping of cochlear nucleus using the single channel surface bipolar electrode, coupled with a 3D navigation system
First, a 961-573J SureTrak2 Active/Passive system (small passive filter and small mount) was attached to the handle section of the prototype microelectrode. This was then linked to a 3D navigation system, and tracer recordings were made (Fig. 12).

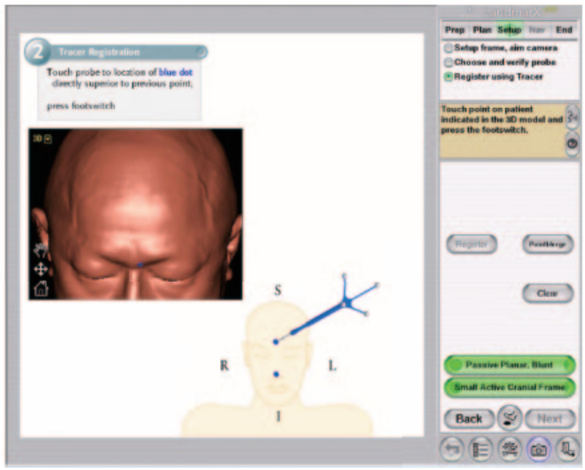


Fig. 12. Tracer recordings
A 961-573J SureTrak2 Active/Passive system (small passive filter and small mount) was attached to the handle section of the prototype microelectrode. This was then linked to a 3D navigation system, and tracer recordings were made.

4.2. Results and discussion

In our research during the year under review, we performed a trial in a patient with an acoustic nerve tumor.

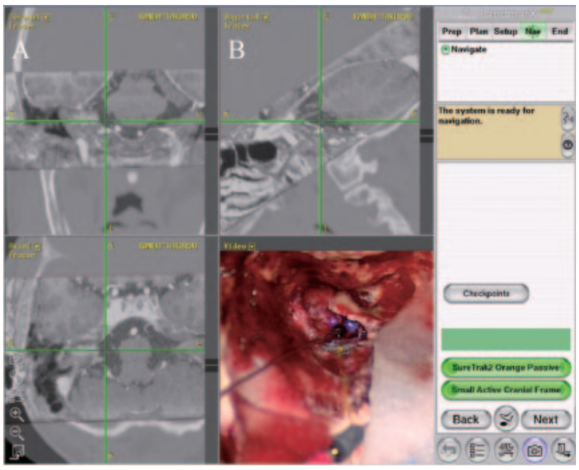


Fig. 13. Electrical stimulation guided by 3D navigation. A, B and C are composite CT and MRI images. A; coronal section. B: sagittal section. C: horizontal section. D: operative field (portion of cochlear nucleus stimulated by the microelectrode).

After surgical resection of the tumor, the navigation system was set up to display the stimulation points on the screen. Then the prototype microelectrode was placed on the auditory nerve and electrical stimulation was applied (Fig. 13). The location of all stimulation points could be recorded. The object is to use the EABR generated by this system to provide a surgeon with the anatomical information needed for him or her to place an ABI on the cochlear nucleus after resection of an NF-II auditory nerve tumor. The margin of error for the probe was 0.5 mm or less, and the navigational accuracy was to within 2 mm.

5. Discussion

Using bipolar stimulating electrodes with an interelectrode distance of 200 μm we carried out electrophysiological mapping of the cochlear nucleus with 1) a 260-channel microelectrode system, and 2) an on-screen virtual mapping system consisting of a single channel microelectrode (bipolar) coupled with a navigation system.

Although the interelectrode distance in the present experiments was double that of our previous study in 2007 (100 μm), nevertheless, we were able to clearly delineate the boundary of the dorsal side of the cochlear nucleus, and the level of precision was considered sufficient to perform the type of brain stem mapping needed for brain stem implants.

A number of studies have been performed to date with regard to the type of electrode used to stimulate the cochlear nucleus. Generally two types of electrodes are available: surface type and needle type. Liu et al. [6] used both types to apply an electrical stimulus to the cochlear nucleus in guinea pig and cat models. They reported that in guinea pigs, needle electrodes had lower threshold values and a wider dynamic range than did surface electrodes. However, from the standpoint of tissue invasiveness, surface electrodes produced no clear morphological changes in the cochlear nucleus either on the surface or internally, whereas implanted needle electrodes have been associated with morphological changes such as reduced neuron density and possible edema of the ventral cochlear nucleus caused by an increase in the surface area of somatic cells [6].

On the other hand, as regards the method of electrode stimulation, most studies have focused on either mono-polar or bipolar approaches. Snyder et al. [6] measured the activity of the inferior colliculus after placement of a cochlear implant. They reported that monopolar stimulation had lower selectivity than bipolar stimulation. They also reported that in bipolar systems, as the distance between electrodes decreases, the frequency selectivity improves, but at the same time the threshold values increase.

The results of the research carried out to this point can be summarized as follows: 1) Surface electrodes are associated with less damage to the cochlear nucleus and are superior to needle electrodes from a safety standpoint; 2) Compared with monopolar electrodes, as the interelectrode distance in bipolar electrodes becomes smaller, the selectivity of the stimulus increases, indicating that reducing the distance between electrodes can improve frequency selectivity. The results of the current study support the clinical use of microelectrode bipolar stimulation.

6. Conclusion

1) Electrophysiological mapping of the cochlear nucleus was carried out using a 260-channel microelectrode system with an interelectrode distance of 200 μm.
2) Clear EABR were obtained, and the electrophysiological mapping was able to clearly delineate the boundaries of the cochlear nucleus.
3) We tested a virtual mapping system for clinical use, consisting of a single channel microelectrode system (bipolar) coupled with a navigation system, and showed that it was possible to use the navigation system to record the location of points that showed a positive response.

These findings provide a strong proof of the concept that EABR data can be used to provide a surgeon with anatomical information when placing an ABI. Clinical applications of this system can be expected in the near future.

Acknowledgements

This study was supported by a grant-in-aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology for fiscal 2007-2008 and Tohoku University Global COE Program "Global Nano-Biomedical Engineering Network Centre."

References

[1] Otto SR, Brackmann DE, Hitselberger WE, Shannon RV, and Kuchta J. Multichannelauditory brainstem implant: update onperformance in 61 patients. *J Neurosurg* **96**, 1063-71, 2002.

[2] Nevison B, Laszig R, Sollmann WP, Lenarz T, Sterkers O, Ramsden R, Fraysse B, Manrique M, Rask-Andersen H, Garcia-Ibanez E, Colletti V, and von Wallenberg E. Results from a European clinical investigation of the Nucleus multichannel auditory brainstem implant. *Ear Hear* **23**, 170-183, 2002.

[3] Behr R, Muller J, Shehata-Dieler W, Schlake H-P, Helms J, Roosen K, Klug N, Holper BM, and Lorens R. The High rate CIS auditory brainstem implant for restoration of hearing in NF-2 patients. *Skull Base* **17**, 91-108, 2007.

[4] Nevison B. A guide to the positioning of brainstem implants using intraoperative electrical auditory brainstem responses. *Adv Otorhinolaryngol* **64**, 154-66, 2006.

[5] Kitahara N. Animal waveforms and their origins: rats and guinea pigs. *ABR Handbook* **14-15**.

[6] Liu X, McPhee G, Seldon HL, and Clark GM. Histological and physiological effect of the central auditory prosthesis: surface versus penetrating electrode. *Hear Res* **114**, 264-274, 1997.

[7] Snyder RL, Middlebrooks JC, and Bonham BH. Cochlear implant electrode configuration effects on activation threshold and tonotopic selectivity. *Hear Res* **235**, 23-38, 2007.