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"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. NO1-DC-8-2102

QUARTERLY PROGRESS REPORT #1

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Summary

We began the evaluation of an array containing 4 discrete iridium microelectrodes, whose lengths were selected to span to tonotopic gradient of the human posteroventral cochlear nucleus. The tips of the microelectrodes are blunt (radium of curvature ~ 6 µm), in order to minimize injury to the brain's vasculature. A custom-designed, hand-held tool was used to implant the arrays into the cochlear nuclei of an unfixed human brainstem and also into living cat lumbosacral spinal cord. In both cases, the insertion velocity was approximately 1 m/sec. The unfixed human brainstem was used as a model for the ability of the electrodes to penetrate the tough glial limitans over the human brainstem, and the feline spinal cord was used as an *in vivo* model for tissue injury and injury to the blood vessels during electrode insertion. The results from both experiments were very encouraging. The microelectrode arrays were inserted into one unfixed human brainstem, a total of 4 times. Each time, the array inserted completely and there was no damage to the microelectrodes. The implanted array demonstrated good stability when the dummy cable was moved from side to side or when it was gently tugged upon. Three arrays were implanted, for 5 hours, into two cat lumbosacral spinal cords. Histologic evaluation of the electrode tracks indicated minimal injury to tissue surrounding the tracks and only a few very small micro-hemorrhages, which were confined to the immediate periphery of the tracks. Neurons close to the tracks appeared normal.

Because the cochlear nuclei are not visible on the surface of the human brainstem surface, we must select another surface landmark for insertion of penetrating electrodes, and this point of entry into the brainstem will determine the orientation of the array within the VCN. Electrode design, including lengths and the distribution of individual stimulating electrodes, will have to take into consideration the point of entry and the angle of penetration into the VCN. The taenia choroidia is a membrane formed by fusion of the ependymal inner surface of the lateral recess with the outer pial surface of the brainstem. At the point where this membrane forms the peripheral opening of the lateral recess (foramen of Luschka), it extends a short distance across the brainstem

surface. The taenia is visible to the surgeon and is routinely used to locate the foramen of Luschka in order to place the surface ABI array into the lateral recess. Computer-assisted reconstruction techniques were used to render semi-serial histologic sections of the human cochlear nuclei and surrounding structures into 3-dimensional reconstructions. This modeling showed that the taenia crosses the posteroventral cochlear nucleus, and that use of this structure as a the point of insertion of the microelectrode array should place the microelectrodes within the population of neurons which carries monaural acoustic information to the inferior colliculus.

I: INTRODUCTION

The work statement of the present contract calls for us to "test the microstimulation system in a deaf human who must undergo surgery for removal of an acoustic neuroma". In this first Quarterly Progress Report of the new contract, we report on several aspects of the project which precede surgical implantation of a microelectrode array, and which are now near solution. Section 2 describes the function of the insertion tool and the prototype clinical microelectrode array that is currently being evaluated. It appears that this tool can be used without further modification during the surgical trials.

Section 3 describes the procedure for specifying the lengths and lateral separation of the microelectrodes comprising the array, based on our decision to use the taenia choroidea as a surface landmark for implantation, and the posteroventral cochlear nucleus as a target. Future QPRs will discuss the process of incorporating the microelectrode array into a hybrid device which will combine the microelectrode array with the currently used surface electrode array. Future QPRs will also discuss protocols for testing the effectiveness of surface and penetrating electrodes in the implant patients.

2: INITIAL EVALUATIONS OF THE PROTOTYPE HUMAN ARRAY AND THE INSERTION TOOL

The insertion tool was designed to allow neurosurgeons to insert arrays of microelectrodes into the human ventral cochlear nucleus, through the restricted aperture of the translabyrinthine surgical opening through the petrous pyramid. A hand-held instrument that is to be used to insert an array of microelectrodes into the cochlear nucleus, or into other brain structures, must protect the array until it is inserted. The instruments must insert the microelectrodes precisely along their axis, so as not to bend the microelectrodes and to avoid slashing through the tissue. It must insert the microelectrodes at a controlled velocity, sufficient to penetrate though the glia-pial layer on the surface of the brain, yet not rupture the microvasculature within the brain tissue.

It must hold the array securely during the entire insertion process, so that tension on the electrical cable trailing from the array does not disturb the axial alignment of the electrodes during insertion, then release the array immediately and automatically after they have been inserted, so that it is not displaced by movement of the surgeons's hand. For the human cochlear nucleus, the microelectrodes must be injected at an angle of approximately 55° relative to the axis of the instrument, which is introduced through the narrow surgical opening through the petrous pyramid, so that the microelectrode tips will be distributed across the tonotopic gradient of the ventral cochlear nucleus. Therefore, the instrument's barrel must be curved. Furthermore, the translabyrinthine surgical aperture has a maximum diameter approximately 2 cm, so the bend in the barrel must have a very small radius of curvature.

These requirements are realized in the hand-held instrument depicted in Figure 2-a. Prior to its deployment, the microelectrode array is enclosed and protected within the end of the barrel. A vacuum of approximately 400 mm of Hg holds the array matrix firmly against the end of a hollow sliding piece within the barrel. The distal end of the barrel is slotted to accommodate the electrical cable attached to the array. (With a vacuum of 400 mm Hg, a cable segment weighing at least 10 grams can be supported). Under visual control, the end of the barrel is placed against the surface of the brain, so as to slightly dimple the tissue. Light finger pressure on the trigger releases the sliding air valve within the body of the instrument. The sliding valve pushes forward a steel wire, which carries the force around the 55° bend near the end or the barrel, and thus advances the sliding piece and the electrode array. The array, still held by the vacuum against the end of the slide, is pushed into the tissue at a specified velocity (0.5 - 2 m/sec). The speed of insertion is controlled by the spring compression adjustment screw, by the amount of vacuum ahead of the sliding air valve in the body of the instrument, and by a viscous-damping speed governor within the instrument's body. When the slide reaches the end of its travel, the air valve within the body of the instrument closes off the vacuum line. At the same instant, a valve port near the end of the barrel opens and these two simultaneous events cause the vacuum within the barrel to collapse within a few milliseconds, cleanly releasing the microelectrode array.

Figure 2-b is a sketch of the prototype microelectrode array intended for implantation into the human ventral cochlear nucleus. It includes 4 discrete iridium microelectrodes, each 75 μm in diameter, which range in length from 1.5 to 3.0 mm. This configuration is based on the human anatomical studies described in the next section, and is intended to bracket the human posteroventral cochlear nucleus. The array also includes a pair of long (4 mm) iridium anchoring pins which are also 75 μm in diameter. These anchoring pins will extend completely through the cochlear nucleus, and they are intended to stabilize the array against modest tension on the attached cable. The functional microelectrodes and the anchoring pins have blunt tips with radii of curvature of approximately 6 μm. This tip configuration is intended to minimize injury to the tissue during insertion. The microelectrodes and the stabilizing pins extend from a 2 mm diameter epoxy matrix.

The hand-held insertion tool was used to implant the arrays into the cochlear nuclei of an unfixed human brainstem and also into living cat lumbosacral spinal cord. In both cases, the insertion velocity was approximately 1 m/sec. The unfixed human brainstem was used as a model for the ability of the electrodes to penetrate cleanly through the glial limitans. The brainstems were obtained from the National Diseases Research Institute. Upon arrival at the House Ear Institute, they were embedded into 5% agar solution and kept under refrigeration at approximately -10°C. Prior to their use, they were thawed, and the agar over the ventrolateral brainstem was dissected away. The microelectrodes were inserted into one brainstem, a total of 4 times. Each time, the array inserted completely and there was no damage to the microelectrodes. The implanted array demonstrated good stability when the dummy cable was moved from side to side or when it was gently tugged upon.

The feline spinal cord was used as a model for tissue injury, and for damage to the parenchymal blood vessels. The dorsal surface of the lumbosacral enlargement is covered by a relatively tough pia mater which is a fair approximation of the glia limitans over the human brainstem. Like the human brainstem, the feline spinal cord contains nuclei embedded in longitudinal fiber tracts, and it is more accessible than is the feline ventral brainstem. Cats tolerate the lumbar dorsal laminectomy very well, so the site is

well suited for chronic as well as acute studies.

The first experiments were acute studies to determine the extent of any microhemorrhages induced by the arrays. One array was implanted into cat CNHA1 and two were implanted into cat CNHA2. Using general anesthesia, the lumbosacral enlargement was exposed by a standard dorsal laminectomy. The dura was opened in a longitudinal slit, and the arrays were inserted into the dorsal surface of the cord at a velocity of approximately 1 m/sec. The array matrices were covered with Gelfoam, the wound was closed, and the cats were maintained under general anesthesia for the next 5 hours. They were then deeply anesthetized with Pentobarbital and perfused through the ascending aorta with ½-strength Karnovsky's fixative. The arrays were removed, the lumbosacral enlargement was resected, embedded into paraffin and sectioned serially at a thickness of 8 μm. Tissue sections were stained with Toluidine Blue (Nissl) or with Hematoxylin and Eosin. In either preparation, red blood cells are easily identified, appearing at iridescent green entities in the Nissl preparations and as pale pink spheroids in the H&E material. In both cases they are well differentiated from the neuropil and from other cell types.

All 21 electrode tracks in the two cats were examined along their entire lengths. The findings were very encouraging. The fiber tracts immediately below the array matrices appeared to be undamaged. Figure 2c shows an oblique section through one of the electrode tracks in cat CNHA2. All of the tracks were surrounded by neutrophilic leukocytes, which is characteristic of the acute phase of any injury, and which appear as small black nodules in these illustrations. There were no red blood cells within the lumen of the track (TR) or in the adjacent tissue. Nearby neurons (N) appeared to be quite normal.

Figure 2d shows the site of the tip (TIP) of one of the microelectrodes in cat CNHA2. There were no blood cells within the track or in the surrounding tissue, and the nearby neurons appeared to be quite healthy. Red blood cells were a rare finding along any of the 21 tracks in these two cats. The largest "microhematoma" associated with any of the tracks is shown in Figure 2e. This section was from the spinal cord of cat CNHA1,which did not perfuse properly with the Karnovsky's fixative. Therefore, the

neurons throughout the spinal cord were dark and shrunken, and this change is unrelated to the insertion of the microelectrodes. However, the cat was still a valid test of any interstitial bleeding which might have occurred between the time that the electrodes were inserted and the time the cat was perfused. A small aggregate of red blood cells is interspersed with the neutrophils at the periphery of one of the track (the aggregate is seen above the patent track in this oblique section). This microhematoma is approximately 150 μm in diameter and appears to be confined to the immediate periphery of the track. Smaller aggregations of red blood cells were seen adjacent to the tracks in 4 of the 163 histologic sections. In 4 other sections, very small aggregates of extravasated red blood cells (10-50 cells) were present in the surrounding tissue, but in no case were these microhemorrhages large enough to have caused any discernable displacement of the tissue.

Figure 2f may provide at least a partial explanation for the minimal vascular injury seen in these animals. The track of one of the 4 mm anchoring pins (TR) and a fairly large blood vessel (VES) are seen in the same section, indicating that the pin's tip had encountered the vessel during its passage through the tissue. However, there was no micro-hemorrhages within the tissue, so the pin's blunt tip apparently pushed the vessel aside. It is encouraging that the blunt-tipped microelectrodes are able to do this, even when inserted at a relative high velocity of 1 m/sec.

3. ANATOMICAL FACTORS PERTINENT TO THE ELECTRODE DESIGN AND SURGICAL LANDMARKS FOR IMPLANTATION

3.0 Electrode dimensions and implantation landmarks

A continuing issue in the development of the brainstem microelectrode array has been the fit of the electrode to its target, the ventral cochlear nucleus (VCN). A major goal of the HEI subcontract is to specify the optimal geometry of a penetrating microelectrode array, including the lengths, spacing and orientation of the stimulating electrodes, based on anatomical studies carried out in human brainstems. Because the cochlear nuclei are not visible on the brainstem surface, we must select a surface landmark for insertion of penetrating electrodes, and this point of entry into the brainstem will determine the orientation of the array within the VCN. Elements of the electrode design, including lengths and the distribution of individual stimulating microelectrodes, will have to take into consideration the point of entry of the array into the tissue, and the angle of penetration into the VCN. During the past year, we modeled electrode insertion through the stump of the cochlear nerve, but these studies revealed several problems with this approach.

The first problem encountered was the frequent absence of a stump of the cochlear nerve after resection of VIIIth nerve tumors from patients with Type II neurofibromatosis (NF2, our prototypic patient population for the intranuclear microstimulation system). In the postmortem material on which the brainstem reconstructions are based, two of four NF2 cases lacked a remnant of the eighth nerve on the brainstem surface. Since a visible nerve stump is present in all of the brainstems of normal subject and in those of subjects who are deaf as a results of etiologies other than NF2, this probably reflects extension of the tumor mass along the nerve and its removal as part of excision of the tumor. A second problem is that rostral angulation of the eighth nerve placed the electrode array, not in the central nerve root area of the VCN, but in its rostral tip. The modeling studies indicated that many of the stimulation sites would lie along the margin of the VCN or outside of its boundaries. Given the restricted field of current spread from microelectrodes, it is unlikely that the marginal sites would provide effective stimulation in an actual implantation. A third

question related to the perceptual usefulness of stimulation of neurons in the rostral tip of the VCN. Our studies of cytoarchitecture of the human ventral nucleus have shown that the rostral tip of the VCN consists mainly of spherical cells. This cell group projects only to the medial and lateral nuclei of the superior olivary complex, where information on interaural differences in stimuli is extracted. The information synthesized by the olivary nuclei is believed to function in spatial localization of stimuli, and thus may not be relevant for speech perception or more global functions. This combination of factors led us to believe that implantation through the cochlear nerve root was not a viable solution.

3.1. The taenia choroidia as surgical landmark

In the search for an alternative route of surgical implantation, we have recently modeled electrode insertion using the taenia choroidea as a surface landmark. The taenia is a membrane formed by fusion of the ependymal inner surface of the lateral recess with the outer pial surface of the brainstem. At the point where this membrane forms the peripheral opening of the lateral recess (foramen of Luschka), it extends a short distance across the brainstem surface. The taenia is visible to the surgeon and is routinely used to locate the foramen of Luschka in order to place the surface ABI array into the lateral recess. The goal of the present study was to determine if a consistent relationship exists between the taenia and the VCN.

Essentially the same procedure was followed as with simulated insertions of electrode arrays through the VIIIth nerve root. Evenly spaced series of stained sections from several normal subjects and from four neurofibromatosis patients were digitized into the PC3D program, a "3-Dimensional" drafting program for the personal computer. Images included the brainstem surface, the ventral cochlear nucleus, pontobulbar nucleus and lateral recess. The PC3D files from each subject were then transferred into AutoCAD for quantitation and three-dimensional reconstruction. Figure 3a shows series of sections through the ventral cochlear nucleus (VCN) of an NF2 patient, and of an age-matched normal subject. The drawings display the brain surface, the upper portion of the foramen of Luschka (FL), ventral cochlear nucleus

(VCN, hatched), pontobulbar nucleus (PBN, stippled) and the seventh and eighth nerves (nVII, nVIIII). An arrow points to the taenia, which is seen in these figures as a short tissue flap extending from the foramen of Luschka. Although the relative position of the anatomical structures is similar in the two cases, there is flattening of the posteroventral cochlear nucleus in the NF2 subject which may have been caused by pressure from the tumor. In these two subjects and all others studied, the taenia is seen to cross the surface of the posteroventral cochlear nucleus and is not associated with the pontobulbar nucleus. A semi-transparent three-dimensional reconstruction of the data from the NF2 subject (Fig. 3b) shows the relationship of the mouth of the lateral recess and the taenia to the ventral cochlear nucleus. The reconstruction confirms that the taenia consistently overlies the VCN and does not cross the pontobulbar nucleus.

3.2. The posteroventral cochlear nucleus as the target

The ventral cochlear nucleus is not homogeneous in its cytoarchitecture. Rather, it consists of clusters of functionally specialized neurons which receive the information carried in the auditory nerve, process it, and relay it to higher auditory centers. Since the current field generated by a penetrating electrode will be confined to the area immediately surrounding the electrode's active site, the site of implantation of the device will determine the type of information transferred to higher auditory centers. This is an important consideration because prosthetic stimulation is intended to create sensations that facilitate speech perception. The cytoarchitectural organization of the human cochlear nuclei is illustrated schematically in Fig. 3c, (based on Moore and Osen, 1979, Moore, 1987). The small cell cap area is particularly prominent in the human cochlear nuclear complex. This area has been shown to contain virtually all of the neurons in the ventral nucleus which are characterized by the presence of the inhibitory transmitters GABA and glycine (Kohlston et al., 1992; Moore et al., 1996). These small inhibitory cells form primarily intranuclear association fibers, and contribute very little to efferent pathways from the VCN. This lack of connections to higher centers should disqualify the cap area as a target of microstimulation. Within the

magnocellular portion of the VCN, retrograde and anterograde transport studies in a variety of mammals demonstrate that the more specialized cell types, including spherical, globular and octopus cells, project to subdivisions of the superior olivary complex (Warr, 1982; Cant and Cassaday, 1986). Neurons projecting to the inferior colliculus are predominantly multipolar cells, a heterogeneous class of neurons located in the central and posterior regions of the nucleus (Adams, 1979; Brunso-Bechtold et al., 1981). These findings, based on anatomical studies, are consistent with the results of physiological experiments involving microelectrode stimulation carried out at HMRI and previously reported in QPR #12 of the previous contract. In all cases of stimulation in the posterior VCN, evoked responses could be recorded from the central nucleus of the inferior colliculus. In a single case of stimulation to the rostral tip of the VCN, no responses in the inferior colliculus could be detected. Thus, within the VCN, we assume than an electrode should target the central and posterior areas of the ventral nucleus where the multipolar cells projecting directly to the inferior colliculus are concentrated.

Because the taenia crosses the posteroventral cochlear nucleus, use of this structure as a landmark should place the electrode array within the population of neurons which carries monaural information to the inferior colliculus. We are currently modeling electrode arrays with lengths of 1 mm, 1.5 mm, 2 mm a2.5 mm and 3 mm, and with a spacing of 0.5 mm between the shafts. Two non-stimulating shafts with a length of 4 mm have been added to the design, to enhance the array's mechanical stability after its insertion into the tissue. As illustrated in Fig. 3c, left figure, we estimate that the active stimulation sites will fall within the central and posterior portions of the VCN.

3.3. Electrode design and the tonotopic organization of the VCN

Though stimulation sites should ideally be confined to the multipolar cell area of the VCN, another goal is to distribute the sites across the tonotopic planes of the nucleus. Subsequent to tumor removal, the peripheral segments of the cochlear nerve axons will degenerate because they have been severed from their somata in the spiral

ganglion. A basic assumption in this project is that the tonotopic organization imposed on cochlear nucleus neurons by the nerve will remain after the axons degenerate. This assumption is bolstered by the fact that some patients with the surface ABI electrode arrays are capable of a degree of pitch discrimination between individual electrodes for many years after resection of the tumor and destruction of the VIIIth nerve.. Figure 3c, right figure, illustrates the course of cochlear nerve axons, and thus the tonotopic planes, in the VCN. It can be seen that there is an upward angulation of the cochlear nerve axon fascicles as they run from the nerve root toward the caudal end of the nucleus. Because the fascicles are angled upward, the shafts of the microelectrode array should cross the tonotopic planes of the posterior VCN roughly perpendicular to the isofrequency laminae.

It is difficult to predict precisely how the electrode stimulating sites will be related to these laminae, but this scattered pattern of stimulation sites should result in activating different parts of the tonotopic axis of the VCN. We thus believe that use of the tania as a landmark will accomplish appropriate stimulation, as well as providing the surgeon with a surface landmark that is not obscured by the tumor or by the process of its removal. Fig. 3d provides a schematic view of the anatomical relationships of a hybrid device consisting of a microelectrode array inserted through the taenia and a surface ABI placed in the lateral recess. We anticipate that a hybrid device of this type will be used in the first surgical trials.

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Work for next quarter

During the past year, we have been conducting animal studies in which we have evaulated the safety and efficacy of stimulation with short-duration, high-amplitude stimulus pulses. These studies will allow us to specify stimulation protocols that can accommodate the existing implantable clinical stimulators, which were designed to drive electrodes that are larger, and which require larger currents than what we have been using with our intranuclear microelectrodes. We have also initiated studies of the effectiveness of a conditioning regimen to reduce the stimulation-induced depression of neuronal excitability. The findings from both of these studies will be described in the January 1 report.

In November, we will begin the chronic implantations of the prototype human array into the feline spinal cord, and the results from the first of these experiments will be described in the January 1 report.

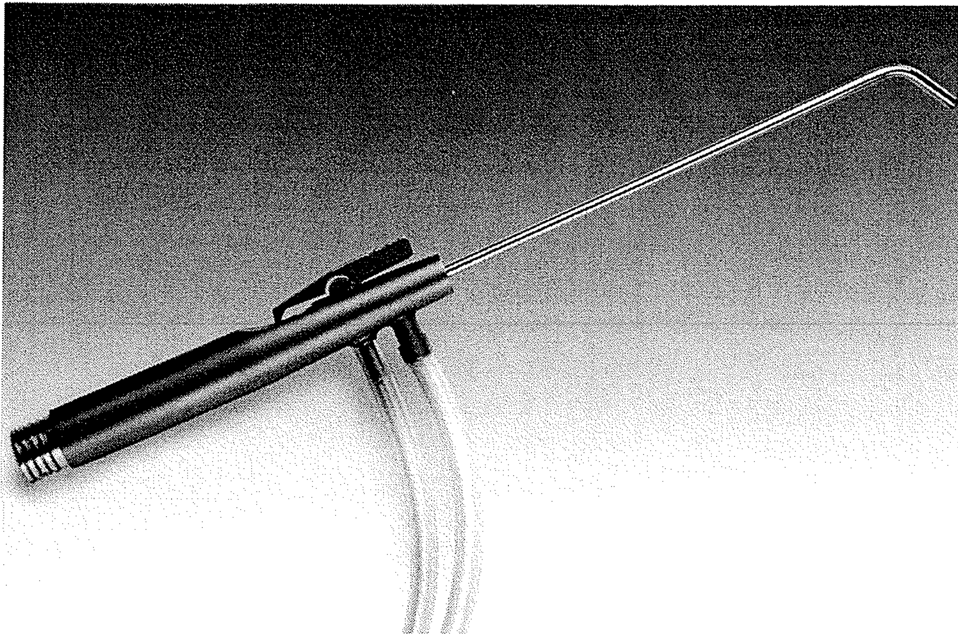

Figure 2a

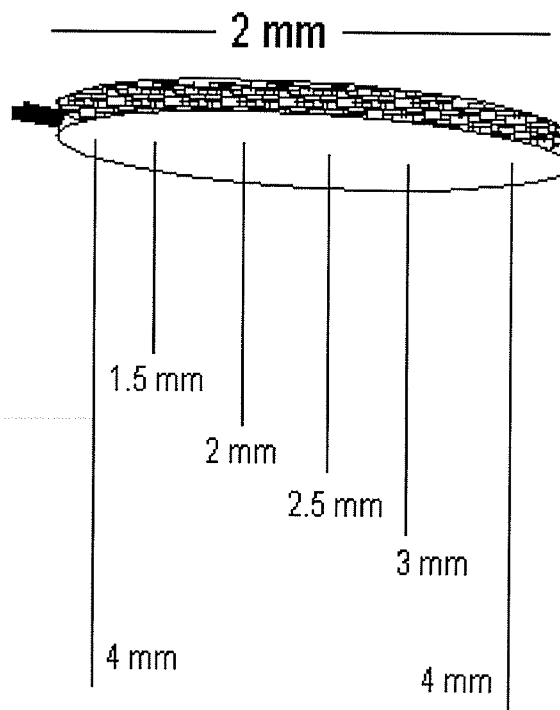

Figure 2b

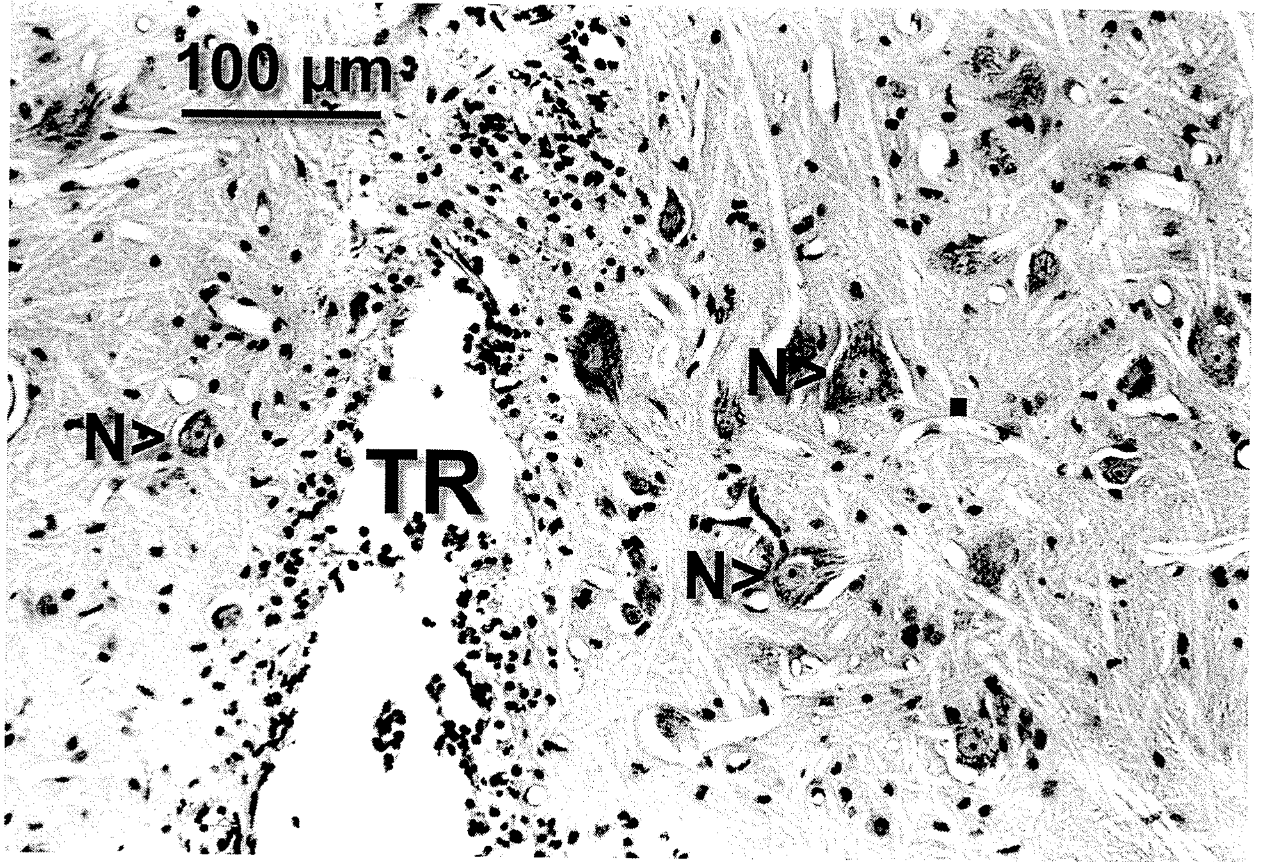

Figure 2c

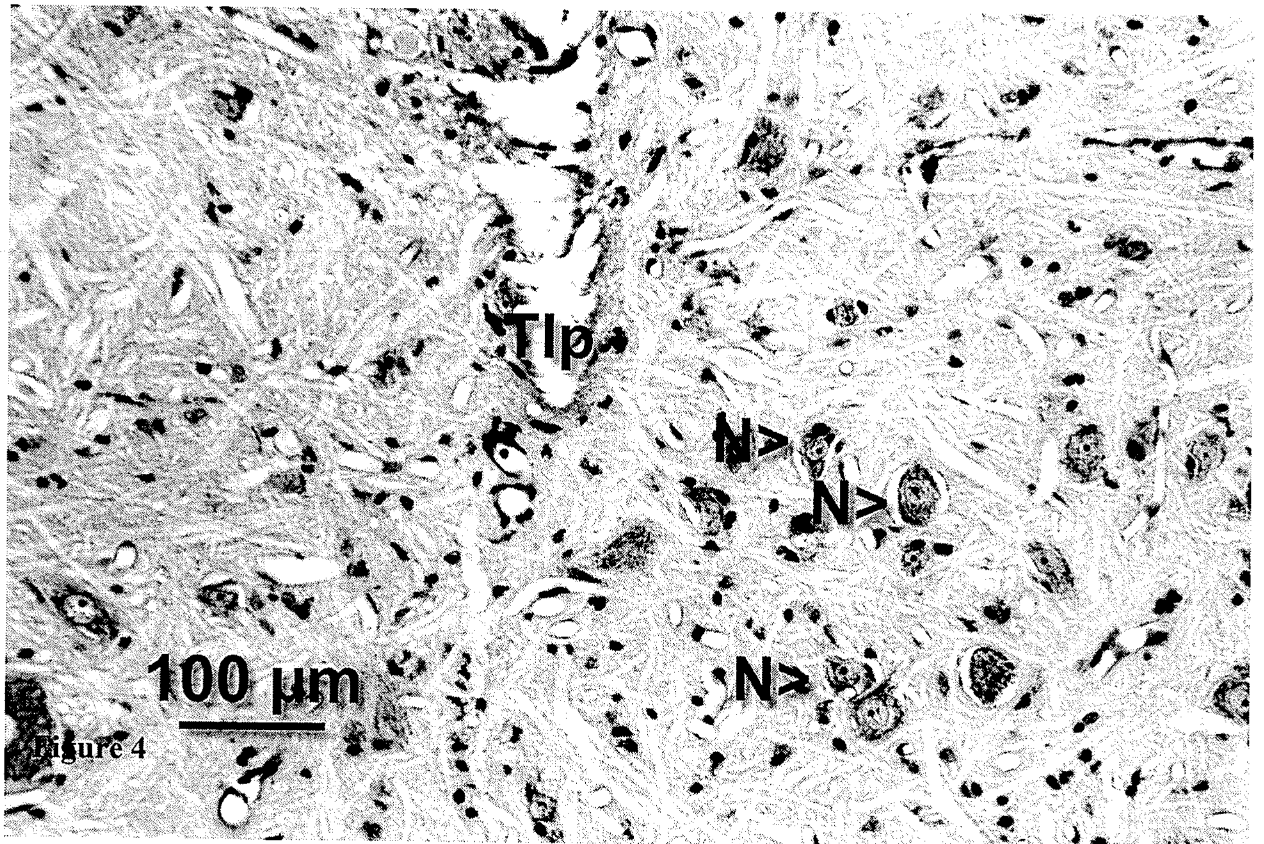

Figure 2d

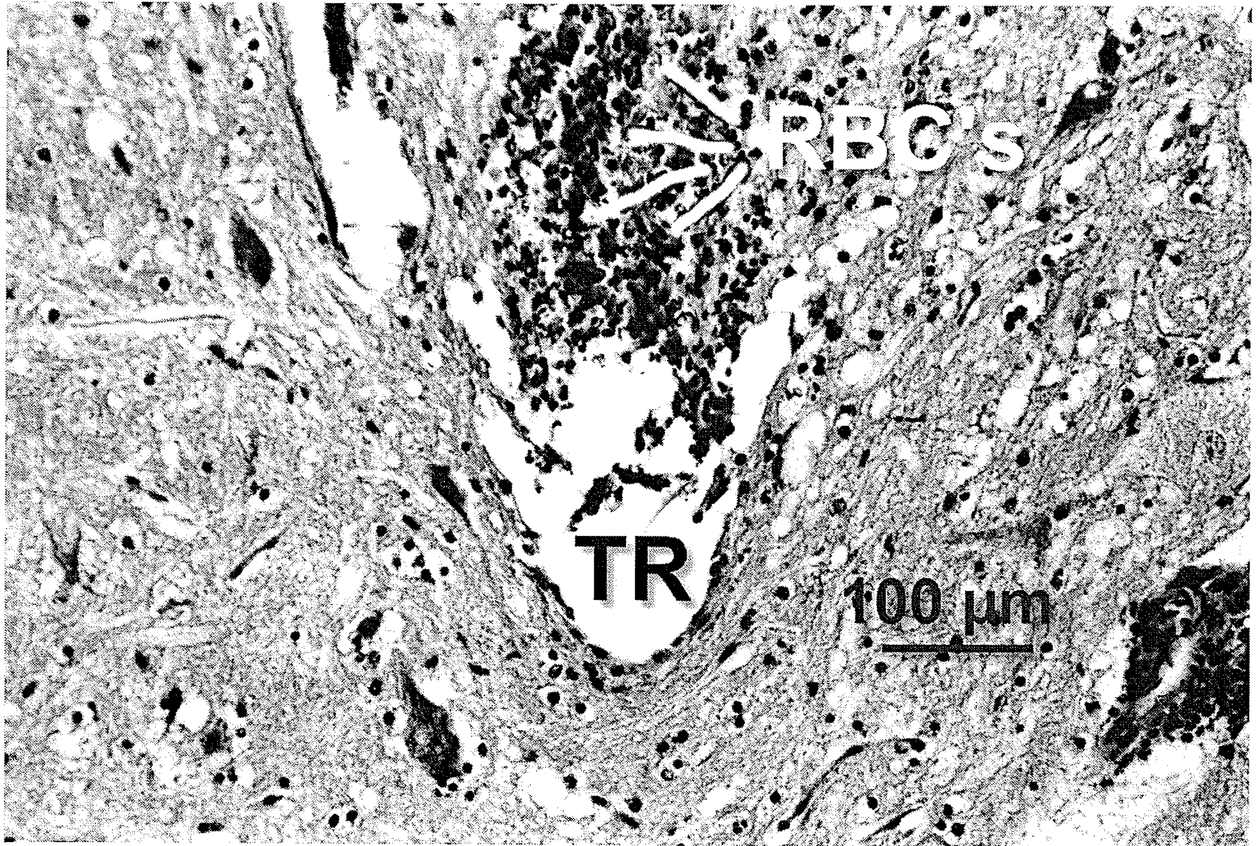

Figure 2e

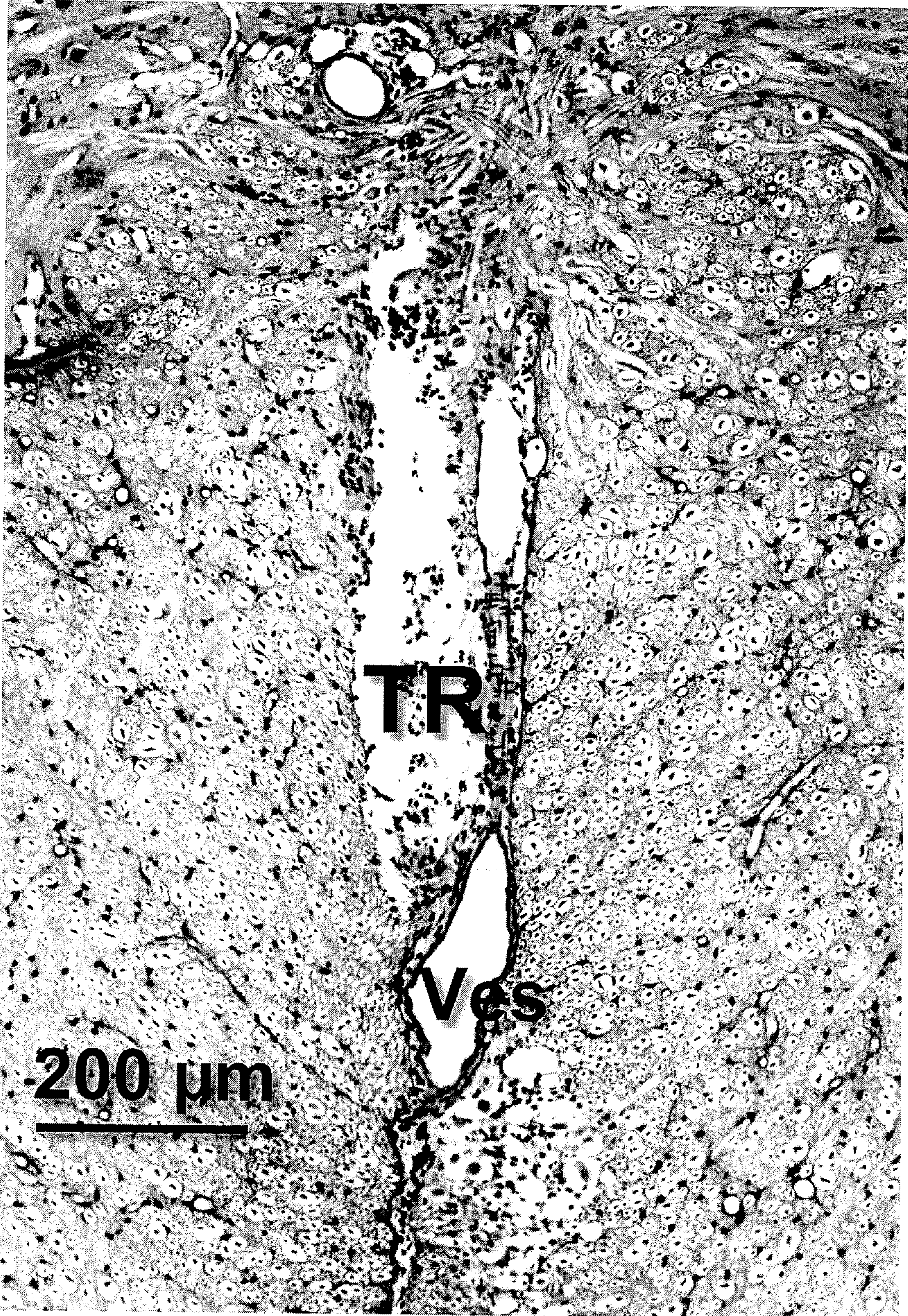

Figure 2f

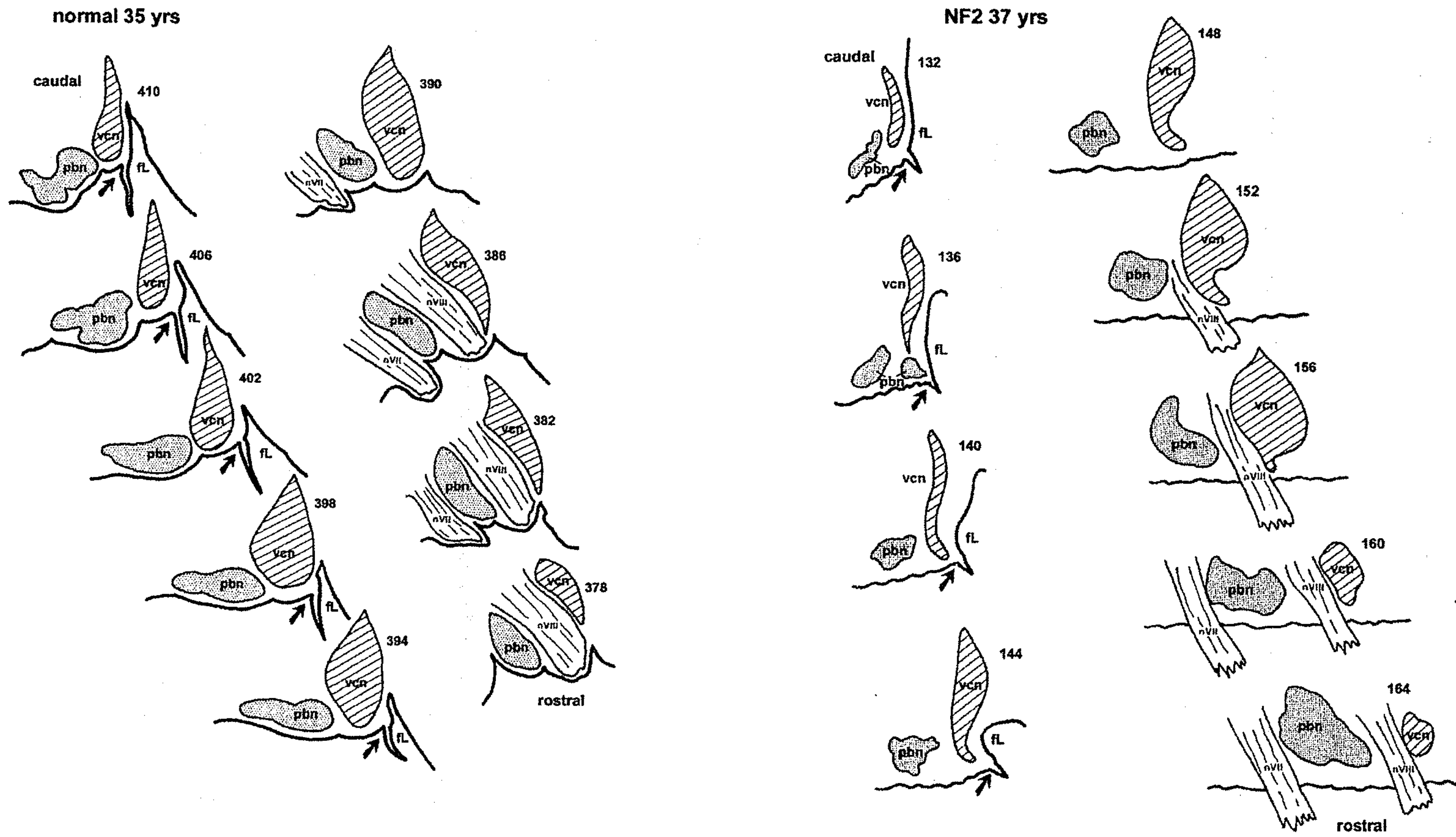

Fig. 3a. Relationship of taenia to ventral cochlear nucleus

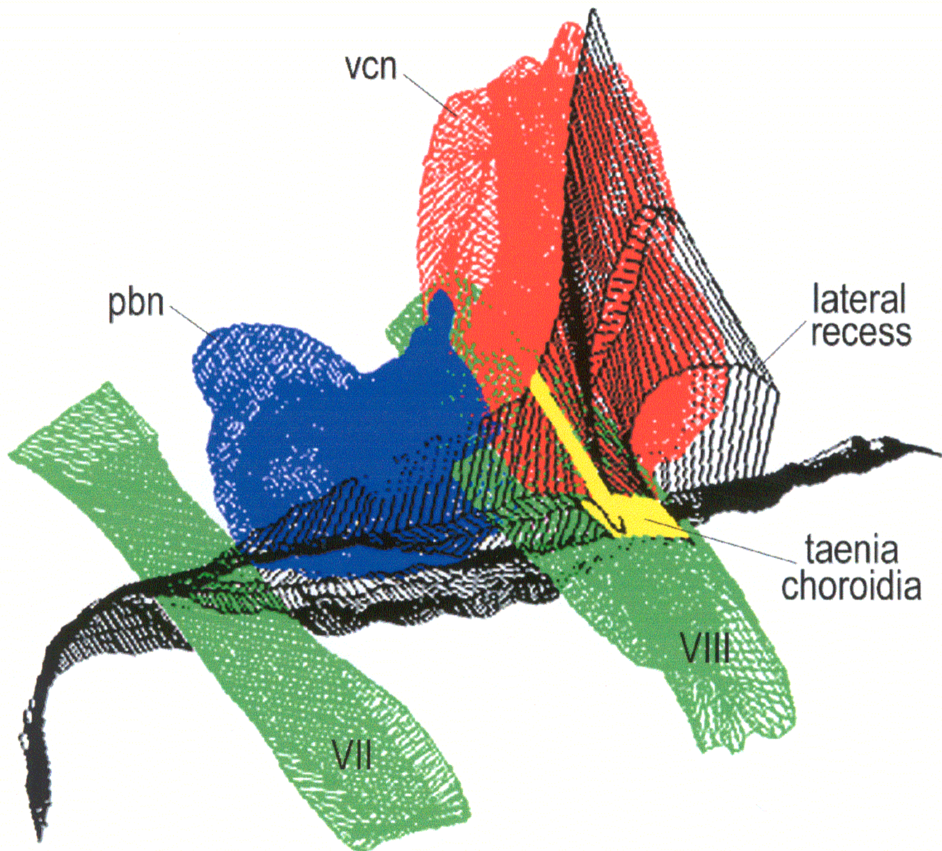

Fig. 3b. 3D reconstruction of taenia and VCN

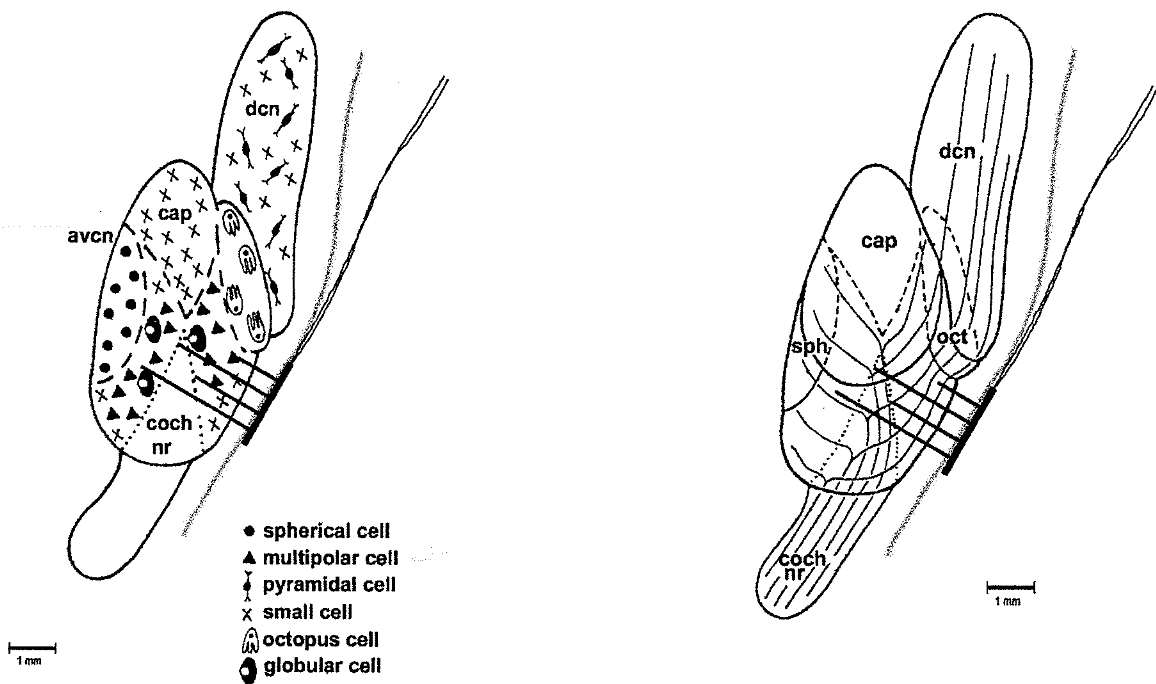

Fig. 3c. Electrode design factors

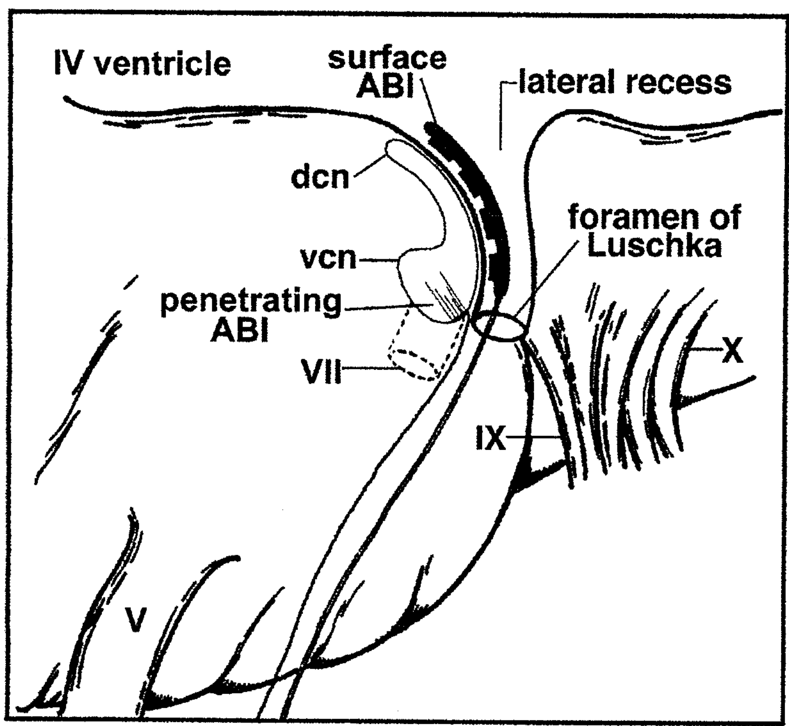

Fig. 3d. Hybrid surface-penetrating device