The Feasibility of a Cochlear Nucleus Auditory Prosthesis Based on Microstimulation

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1.0 Overview

These studies are a continuation of our program to develop an auditory prosthesis based on multisite microstimulation in the ventral cochlear nucleus, for profoundly deaf patients who cannot benefit from an cochlear implant. One of the goals of the work being performed at HEI under this contract is to investigate the neuroanatomical details of the human cochlear nucleus that are relevant to the use of the intranuclear auditory prosthesis. Previous QPRs have concentrated on aspects of implanting the array into the nucleus. One issue has been the design of a tool to carry the array and insert it into the brainstem. We have used whole-head, 3-dimensional computer modeling to determine the dimensions of such a tool, and prototype tools are now being constructed. A second issue has been the ability of the various types of microelectrodes to penetrate the overlying glial layer of the brainstem in the area of the cochlear nuclei.

Another goal of our subcontract is to specify the optimal geometry of a penetrating microelectrode array, including the size and spacing of the stimulating electrodes. In section 2.0 we consider the constraints placed on design of a microelectrode array by the internal organization of the human cochlear nuclear complex. One question is whether an array of staggered electrodes inserted into the human cochlear nuclear complex will cross the tonotopic gradient and produce sensations differing in perceived pitch. In Section 2.1 we discuss the axonal organization of the human cochlear nuclei from this perspective. A second question is whether microstimulation in the cochlear nuclei will convey the percepts that are necessary for speech recognition. In Section 2.2 we consider the cytoarchitectural organization of the human cochlear nuclei and its implications for information transfer to higher auditory centers. In addition, we have obtained the brainstem of a second patient with neurofibromatosis type 2 (NF2) and with large bilateral tumors of the 8th nerves. Histological processing of this brainstem has been completed, and we have completed PC3D/AutoCAD computer modeling of

insertion of three types of multisite electrode arrays into the ventral cochlear nucleus. The results are similar to those previously obtained from three subjects with eighth nerve tumors. The implications of the findings in sections 2.0 and 3.0 for electrode design are discussed in section 4.0. Factors determining the length and spacing of the microelectrodes in the array are discussed in section 4.1, and considerations relating to electrode position in the ventral cochlear nucleus are discussed in section 4.2.

2.0 Anatomical Factors affecting Design and Placement of the Microelectrodes

Currently, testing of multisite microelectrode arrays in the cat cochlear nucleus is being carried out at HMRI, in order to determine if selective activation of different portions of the tonotopic gradient can be achieved. The data indicates that selective activation of tonotopic planes within the inferior colliculus can be achieved by individual stimulating electrodes in the ventral nucleus (McCreery et al, in prep.). Can the cat data be extrapolated to the design of an auditory prosthesis for clinical use in humans? To answer this question, it is necessary to consider the similarities and differences in the cochlear nuclei of cat and man. We will compare two organization features of the human and feline nuclei which affect electrode design and placement, namely, the tonotopic (cochleotopic) representation of auditory nerve axons, and the distribution of distinct populations of relay neurons.

2.1 Axonal Organization of the Human Cochlear Nuclei

The pattern of branching of the auditory nerve input within the cochlear nuclei is very similar in all mammalian species. This sequence, with axons from the basal cochlea projecting dorsally in the nucleus and axons from the apical cochlea projecting ventrally, has been observed in both the dorsal and ventral nuclei in every species investigated to date (reviewed by Moore, 1986). In particular, work done in the cat has demonstrated the cochleotopic sequence of auditory nerve axons in the cochlear nuclei (Lorente de No, 1933; Powell and Cowan, 1962; Sando, 1965; Osen, 1970; Arnesen and Osen, 1978). Recently, very precise mophometric data on dimensions of the

cochleotopic planes in the feline ventral cochlear nucleus has been published by Snyder et al. (1997). Electrophysiological recordings (Rose et al., 1959, Bourke et al, 1981) and axonal transport studies (Fekete et al, 1984) have confirmed that the cochleotopic sequence of axons produces a tonotopic gradient in which high acoustic frequencies are represented in the dorsal-most portion of each nuclear subdivision and low frequencies are represented in the ventral portions. Since recording studies cannot be done in humans, the tonotopic sequence of axons in the human ventral nucleus is assumed to be homologous to that of other mammals.

Information about the anatomy of the auditory nerve in the human cochlear complex comes from the studies of Moore and Osen (1979a,b) and from observation of histologically processed sections through the nucleus. Figure 1 illustrates material from a brainstem which was embedded in celloidin. Due to enlargement of the cerebellar peduncles in humans, the anterior end of the cochlear nucleus complex is rotated laterally by about 30°. The brainstem from which the microphotographs in Figure 1 were taken was sectioned along the long axis of the cochlear nuclei, in the rotated sagittal plane, as shown in the sketch of the brainstem as seen from its dorsal surface(small insert) . The sections were stained with Cresyl violet and iron hematoxylin to demonstrate both cells and myelinated nerve fibers. The section through the dorsal nucleus (DCN) lies somewhat more lateral to the ventral nucleus, but the relative position of the two nuclei is accurately represented. In addition, the microphotographs illustrate that superficial posterior surface of the nuclei is covered by the pontobulbar body (PBB).

The axonal organization can be seen in the larger drawing and in the microphotographs. Afferent fibers of the auditory nerve bifurcate within the nerve root (ANR) to form ascending branches to the anteroventral division of the complex (AVCN) and descending branches to the posteroventral (PVCN) and dorsal (DCN) divisions. The direction of the auditory nerve axons within the three divisions of the complex is

indicated by arrows. Within the ventral nucleus, the axons bifurcate and diverge at an angle of about 90°, and an ordered sequence of axon fascicles crosses the AVCN and PVCN. The dorsoventral elongation of the human nucleus makes the axonal planes more oblique than in the cat, but the organization of the ascending and descending auditory nerve branches is so similar to that in other mammals that we assume a similar tonotopic organization, with high tonal frequencies represented dorsally and low frequencies ventrally.

Although most of the ventral nucleus consists of cells lying within the field of the ascending and descending auditory nerve branches, there is a cap area which lies outside the field of the auditory nerve fibers. This cap area lies mostly dorsal to the main portion of the nucleus, but extends down along its medial and lateral margins. It is innervated by long collaterals of the main branches of the auditory nerve (Feldman and Harrison, 1969; Osen, 1970), and is closely related to systems of association axons which interconnect the dorsal and ventral nuclei (Lorente de No, 1933). Electrophysiological recordings in the cap area of the cat (Bourk, 1976) demonstrated that its cells have physiological properties which are quite different from units in the main subdivisions of the ventral nucleus, and do not show a clear tonotopic sequence. These findings suggest that the cap area would not be an appropriate site an intranuclear auditory prosthesis.

In the dorsal nucleus of carnivores and rodents, descending auditory nerve branches twist as they enter the nucleus so that axons from the basal portion of the organ of Corti are located dorsally and axons from the apical portion are located ventrally (reviewed in Moore, 1986). Thus, in non-primate species, the cochleotopic axis of the DCN is oriented parallel to that of the VCN, with the highest frequencies located dorsally and the lowest frequencies ventrally. This cochleotopic pattern is also seen in anthropoid primates such as the squirrel monkey (Moskowitz and Liu, '72). In man, however, the descending branches do not turn to run parallel to those in the ventral nucleus. As

seen in Figure 1, axons in the dorsal nucleus run from ventral to dorsal, parallel to the long axis of the nucleus. If the preterminal unmyelinated portions of these fibers do not deviate from the course of the main axons, then the cochleotopic axis of the human DCN would be expected to be aligned across the long axis of the nucleus. The basis for this difference in axonal organization is the progressive loss of lamination of the dorsal nucleus which occurs across primate taxa (Moore, 1972). A consequence of this change is that a single microelectrode shaft placed within the dorsal nucleus would lie along a single tonotopic plane, i.e., parallel to the tonotopic gradient rather than orthogonal to it. Multielectrode arrays might access different tonotopic planes because of their separation in the mediolateral and rostrocaudal dimensions of the nucleus, but this would be critically dependent upon the exact location of the array, and is an addition reason for not selecting the DCN as a target for in intranuclear array..

2.2 Cytoarchitecture of the Human Cochlear Nuclei

Retrograde and anterograde transport studies in a variety of mammals demonstrate that the neurons projecting to the inferior colliculus are predominantly multipolar cells, a heterogeneous class of cells located in the central region of the nucleus, surrounding the nerve root (Adams, 1979; Brunso-Bechtold et al., 1981). The more homogeneous cell types, including spherical and octopus cells, project to lower centers, especially in the superior olivary complex (Warr, 1982; Cant and Cassaeday, 1986). Thus, within the VCN, we assume than an electrode should target the central area of the ventral nucleus where neurons projecting directly to the inferior colliculus are concentrated. The dorsal nucleus contains a large population of fusiform cells which project directly to the inferior colliculus (Osen, 1972), but its function and altered tonotopic organization are reasons for not considering it a site for microstimulation.

Analyses of the cytoarchitecture of the human cochlear nuclei (Moore and Osen, 1979a,, Moore, 1987) include comparisons of cell types with those of the cat (Osen, 1969) . In Nissl sections of the human ventral nucleus, the same cell types are

encountered as in the cat but in somewhat different proportions. In man, as in the cat, the ventral nucleus can be divided into a rostral area of spherical cells (sph), a caudal area of octopus cells (oct), and an intervening central region where globular cells, multipolar cells and small cells are intermingled (cent). Although homologous classes of neurons are present in the cat and in humans, the relative proportion of the various cell types differs. In particular, the relative numbers of spherical cells and octopus cells appear to be less in the human ventral nucleus, probably due to differences in their target nuclei in the superior olivary complex (Moore and Moore, 1971). Thus the central area constitutes a relatively larger share of the human ventral nucleus, extending the full dorsoventral height of the nucleus and most of its anteroposterior length, and presumably including a full representation of the tonotopic gradient. These phylogenetic differences serve to increase the volume of the target area for an intranuclear prosthesis in the human ventral nucleus.

The size of the cap area varies across mammalian species, from a very thin layer in rodents, increasing in size in carnivores, and constituting an increasingly large part of the ventral nucleus in primates. The cap area has been shown in the cat and baboon to contain virtually all of the neurons in the ventral nucleus which contain the inhibitory transmitters GABA and glycine (Kohlston et al., 1992; Moore et al, 1996). These GABA- and glycinergic cap cells are believed to form intranuclear association fibers. It is clear that they do not form ascending connections to higher auditory centers because very few GABA- or glycine-positive axons leave the cochlear nuclei in the trapezoid body (Moore et al., 1996). This lack of connections to higher centers in an additional reason for eliminating the cap area from consideration as a target for an intranuclear auditory prosthesis..

3.0 Modeling from the brainstems of patients with NF2

In QPRs #2 and #4 of this contract, we presented three-dimensional reconstructions of the cochlear nuclei of several acoustic neuroma patients. These reconstructions

include the brainstem surface and external features which could serve as landmarks for surgical implantation of the array. In QPR #6, we used AutoCAD to simulate electrode placement, using the eighth nerve stump as the insertion point. Our initial assumption was that the inserted array would consist of single silicon probe with several electrode sites. However, when we attempted to insert the silicon probes into unfixed human brainstems, they snapped off at the base of the shafts, without penetrating the pial-glial layer. In these tests, multi-shaft iridium electrode arrays successfully penetrated the brainstem surface, and therefore these have been included in this modeling study. We here report AutoCAD modeling of a multi-site thin-film silicon probe, and two sizes of arrays of iridium electrodes. In the model, all were"inserted" into the rostral VCN through the eighth nerve root (Figs. 2-7). The computer reconstruction was based on histologic sections of the brainstem of a patient with neurofibromatosis type 2 (NF2), and with large bilateral tumors. As in the previous three subjects, drawings were made from stained sections through the cochlear nuclei, and the brainstem surface and margins of the cochlear nuclei were digitized into the PC3D program. In this subject, the stump of the eighth nerve was visible on both sides of the brainstem.

Figures 2 and 3 illustrate a single shaft silicon probe with 4 stimulating sites. Figure 2 is a reconstruction of the left cochlear nuclear complex and Figure 3 of the right nucleus. Both figures include a frontal view of a wire-frame reconstruction of the section of the ventral nucleus overlying the cochlear nerve root (crosshatched area). The electrode has a total length of 5 mm, but because of the tissue overlying the ventral surface of the ventral nucleus, only about 4 mm of the shaft actually lies within the nucleus. The electrode does not penetrate the dorsal tip of the nucleus, which is the cap area. The silicon probe is shown in five positions, including a 0° position (parallel to the brainstem midline) and also when angled either 15° or 30° toward or away (-15°, -30°) from the midline. The model illustrates that even moderate misdirection of the probe can place part of the shaft outside of the nucleus. In general, only the 0° and 15° or -15° positions place most of the shaft within the nucleus. Figures

2 and 3 also illustrate a lateral view of a wire-frame reconstruction of the entire cochlear complex (ventral and dorsal nuclei). This view illustrates that inserting the array into the nerve root places the array in the most rostral aspect of the VCN.

Because of the failure of unreinforced silicon probes to pierce the brainstem surface, we have tested and modeled four-shaft iridium microelectrode arrays. Our first estimate of electrode length and spacing produced a composite electrode array with shafts 2 mm to 5 mm in length and spaced 1 mm apart. An array with these dimensions has been used in experiments on unfixed human brainstems (reported in QPR #4). Figures 4 and 5 shows the modeled "insertion" of an array of this type into the right and left cochlear complexes of the NF2 patient. As in Figures 2 and 3, the frontal view illustrates only the electrode array and the portion of the ventral nucleus overlying the nerve root (crosshatched area). The entire nuclear complex is shown in relation to the electrode array, in the lateral and top views. It is apparent that all of the shafts lie at the margin of the ventral nucleus or outside it, and thus might not be effective in stimulating the nucleus. Similar results were reported previously for the three subjects with 8th nerve tumors.

The results from the first modeling of the HMRI electrode array led us to consider a design with shorter and more closely-spaced microelectrodes. Figures 6 and 7 illustrate this more compact design, with microelectrodes 1 mm, 1.5 mm, 2 mm and 2.5 mm in length, and spaced 0.5 mm apart. A central, non-simulating shaft with a length of 5 mm was added to the design to help to stabilize the array after insertion into the tissue. In the frontal view, it appears that all four stimulating tips would lie within the VCN at different isofrequency planes, but they do not span the entire frequency gradient (most lie in portion corresponding to low and middle frequencies). None of the tips extend into the dorsal-most cap area of the ventral nucleus. In the lateral and top views, it appears that three of the four electrodes lie within the ventral nucleus on both the right and left sides. Thus, of the two iridium arrays, the more compact

electrode array seems to offer a higher probability of placing several stimulation sites within the VCN.

4.0 Design and Placement of a Cochlear Nucleus Electrode

In the next section, we consider the implications of these and previous findings for the design and implantation of a microelectrode array intended to access the tonotopic gradient in the human cochlear nucleus.

4.1 The length of the microelectrodes

Previous work has provided information on the size of the cochlear nuclear complex in normal-hearing subjects and in the NF2 patients in which the electrode array would be used. The dimensions of the ventral nucleus, as seen in the schematic drawing in Figure 1, are 3 mm along its dorsoventral axis (not including the cap area). Within this 3 mm lies the entire spectrum of tonal frequencies processed by the human ear. These dimensions were, however, obtained in Moore and Osen's study of the normal human cochlear complex (1979a,b). They are consistent with the body of data on the dimensions and volume of the human cochlear nuclei that we have gathered in normal and profoundly deaf subjects. These early studies (Contract 1989-92, QPR #8) established that the volume is not different in adult normal and deaf subjects. We later determined (Contract 1992-95, QPR #6) that the volume of the cochlear nuclei in an NF2 subject was reduced to one-half to two-thirds of that of the other deaf subjects. This reduction is probably due to complete postoperative loss of the auditory nerve in acoustic neuroma patients, while other profoundly deaf subjects retain 3000 to 9000 auditory nerve axons to form a plexus of neuropil within the nuclei (Moore et al, 1997). This loss of neuropil in neuroma subjects presumably reduces the size of the nucleus without distorting the internal organization of the nucleus. It does, however, reduce the size of the target area of the ventral nucleus to approximately 2 mm to 3 mm along any dimension. We assume that the tonotopic gradient is distributed across the 2-3 mm dorsoventral extent of the ventral nucleus.

4.2 The problem of proper electrode position

This reduced size of the target makes the proper positioning of the electrode array even more critical. However the neurosurgeon views the brainstem through the 2 x 2 cm translabyrinthine surgical opening. An obvious problem is the fact that the surgeon will have difficulty determining the plane of the brainstem midline when there has been displacement of the brainstem by the tumor mass. Displacement of the brainstem relative to the skull means that external bony landmarks cannot be used for guidance. This has raised issue of use of landmarks on the surface of the brainstem to guide the arrays into the cochlear nuclei. In both cat and man, the cochlear nuclear complex lies on or near the surface of the brainstem at the pontomedullary junction. In the cat, the body of the VCN is almost entirely superficial, lying immediately deep to the pial surface of the brainstem and forming a prominent protuberance on its surface. Only the most rostral tip of the nucleus is covered by the cerebellar flocculus. In man, the body of the VCN is covered to a variable degree by the flocculus and by the fibers of the middle cerebellar peduncle (Moore and Osen, 1979a). For the main portion of the ventral nucleus, the only visible landmarks are the stump of the eighth nerve (QPR #6, this contract) and the taenia, a structure near the external opening of the lateral recess.

The findings in the latest NF2 patient confirm previous results from subjects with unilateral and bilateral tumors, and illustrate that use of the auditory nerve as a guide for implantation will place the electrode, not in the central area of multipolar cells, but into the most rostral part of the ventral nucleus. The anatomical basis for this is the fact that the auditory nerve approaches the nuclear complex from its rostral aspect, and is superficial (visible on the brainstem surface) over the rostral tip of the nucleus. This rostral angulation of the nerve can be observed in the inset drawing and photograph in Figure 1. Our review of cytoarchitecture of the human ventral nucleus made it clear that the rostral aspect of the nucleus contains mainly the spherical cells. In QPR #4 of the present contract, we reviewed the evidence that spherical cells project only to the

main nuclei of the superior olivary complex, where information on interaural differences in stimuli is extracted. The neural processing in the olivary nuclei is believed to function in spatial localization of sound and thus may not be useful for monaural speech perception.

5.0 Conclusions

One goal of the present stage of contract work is a more precise definition of the target area for an intranuclear auditory prosthesis, so that the configuration of the microelectrode array can be specified more precisely. Anatomical and functional studies in other species give reason to eliminate the dorsal nucleus and cap area as targets for microstimulation. The internal axonal organization of the human dorsal nucleus provides further grounds for not targeting the dorsal nucleus, since the electrodes would not be distributed across the tonotopic gradient. Within the ventral nucleus, we have reason to assume that there is a full representation of auditory frequencies across the dorsoventral dimension of the nucleus. However, our previous studies suggest that in a patient with NF2, this gradient will be compressed into a somewhat smaller space (approximately 2-3 mm in width). Our best evidence to date suggests that a microelectrode array should place several stimulating sites within a 3 mm linear dimension and should allow approximately 1 mm for the non-nuclear tissue overlying the ventral nucleus.

The target area is further limited by the fact that the ventral nucleus is not homogeneous in its cytoarchitecture. Our knowledge of projections of the various cell populations implies that electrode arrays should avoid the spherical and octopus cell areas and should be inserted into the central region of the nucleus where multipolar/stellate cells are concentrated. Given the relatively small volume of tissue that is the optimal target area, how can we insure accurate electrode placement? In modeling the single shaft silicon electrode in several positions, it was clear that a small error in the angle of insertion could place most of the electrode sites outside of the

cochlear nucleus. We modeled the multi-shaft iridium electrode only for one angle of insertion, but certainly a faulty angle of insertion could place several of the electrode tips outside of the ventral nucleus. Even if stimulating sites lie within the ventral nucleus, our modeling suggests that use of the eighth nerve stump as a surgical landmark will place the array in the most rostral area, containing primarily the spherical cells. If spherical cells do not relay perceptual information to the inferior colliculus, microstimulation here will be ineffective as an auditory prosthesis. The taenia, a structure visible on the surface of the brainstem, overlies part of the posteroventral nucleus which contains most of the multipolar cells that project to the inferior colliculus. Also, the posteroventral nucleus is broader than the AVCN, and therefore the angle of insertion of the microelectrodes will be less critical. Future efforts will investigate the use of the taenia as a landmark for the placement of a microelectrode array.

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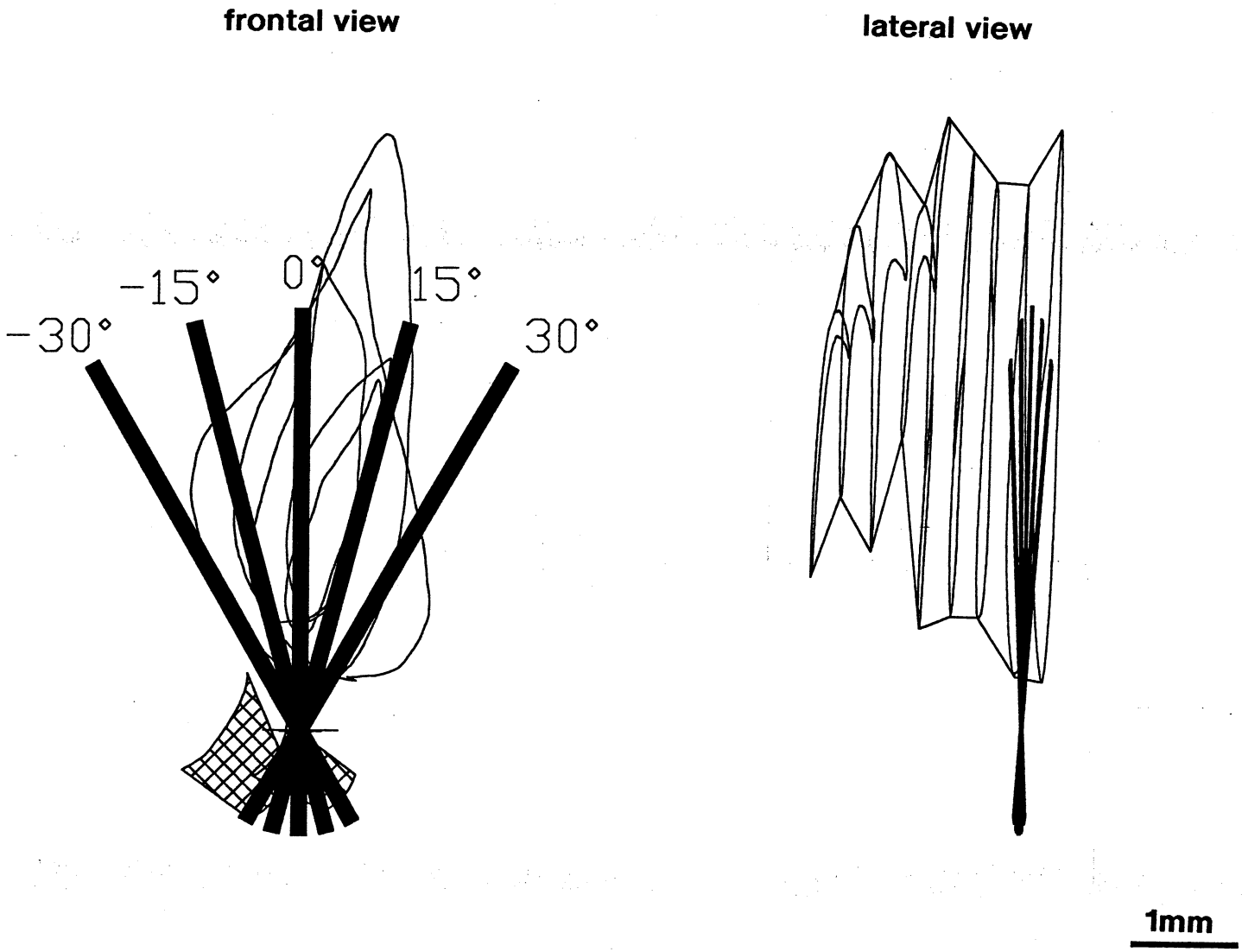
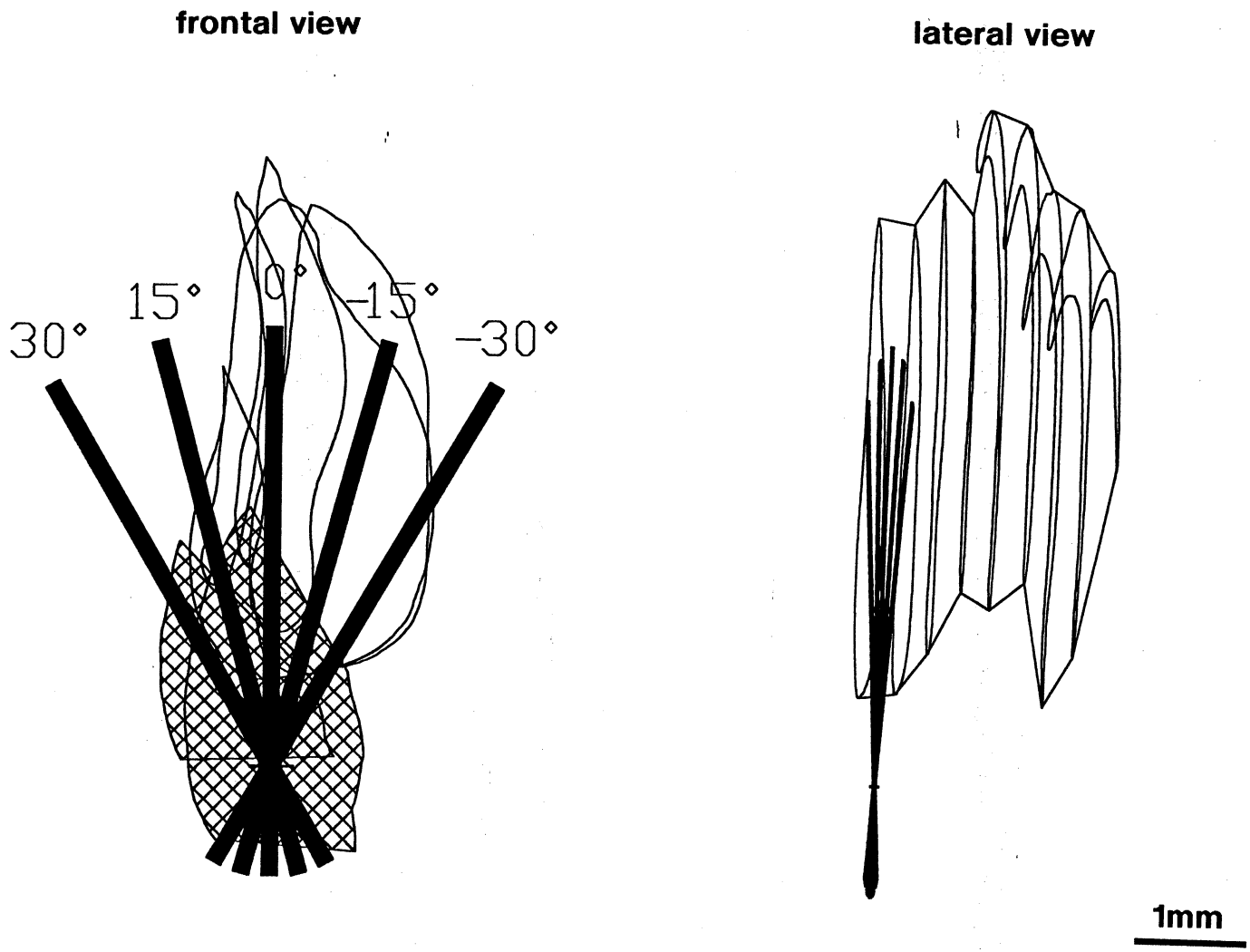


Fig 2. Photolithographic array, single shaft



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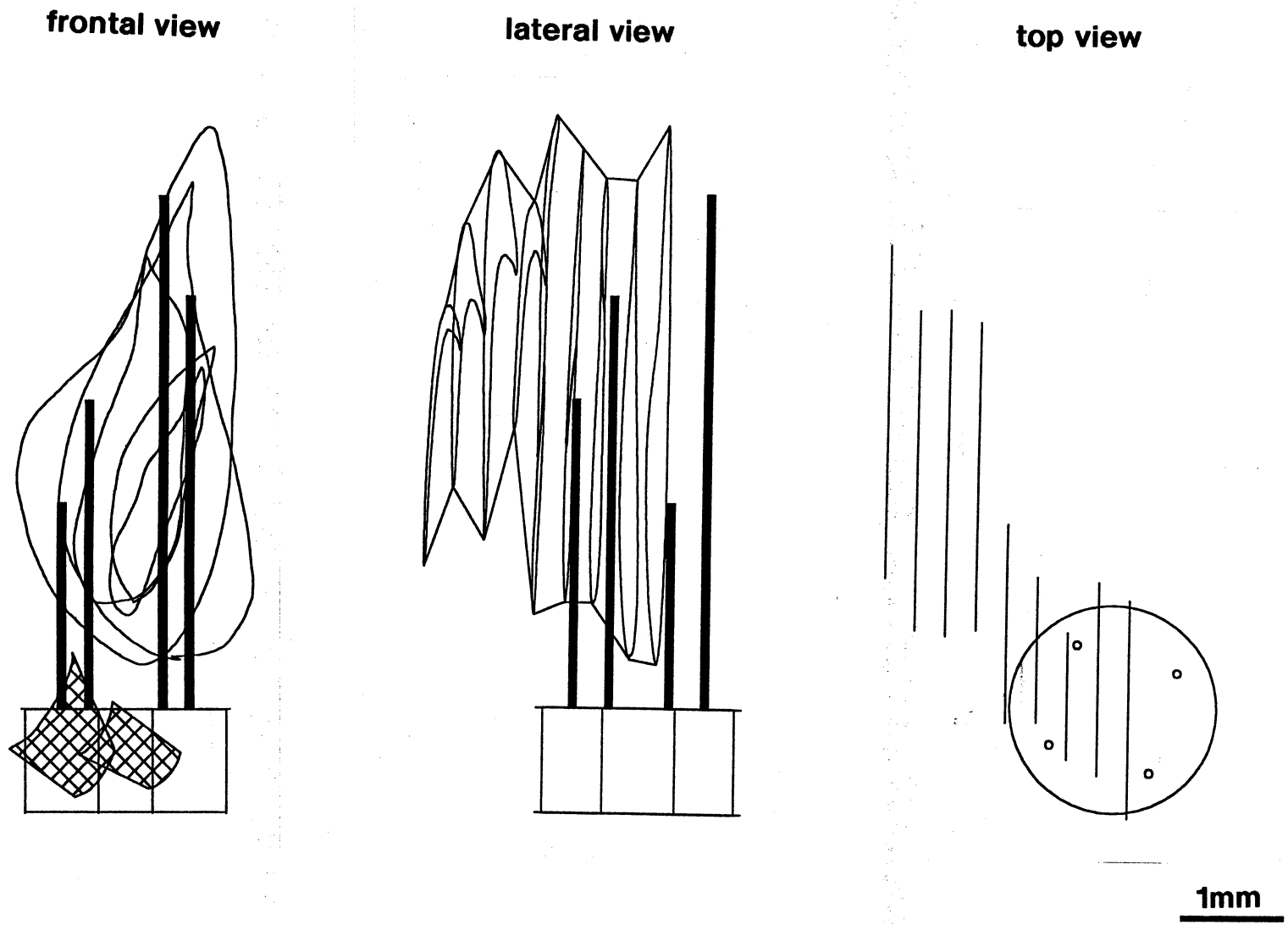

Fig 4. 4 iridium electrodes, 2–5 mm

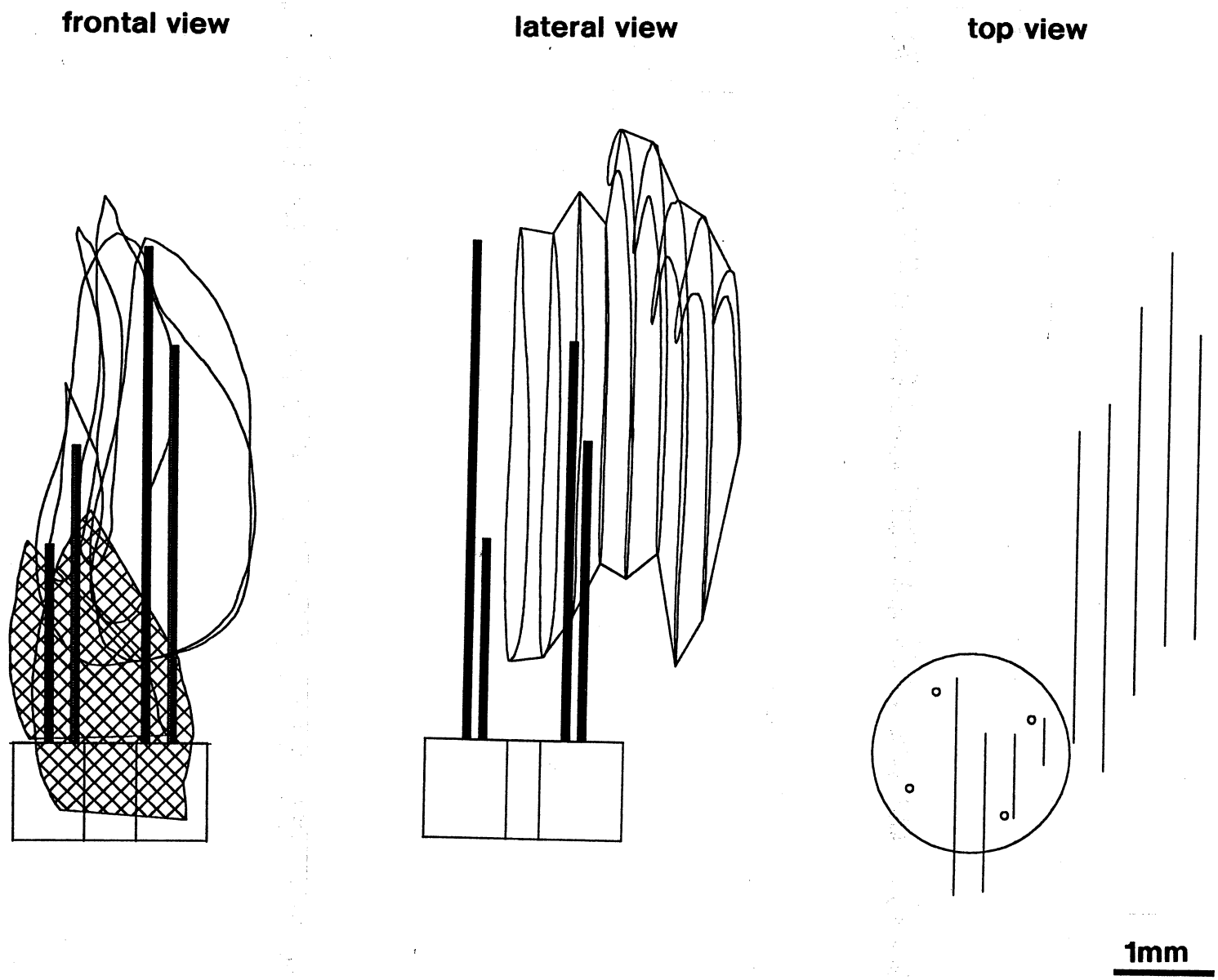

Fig 5. 4 iridium electrodes, 2–5 mm

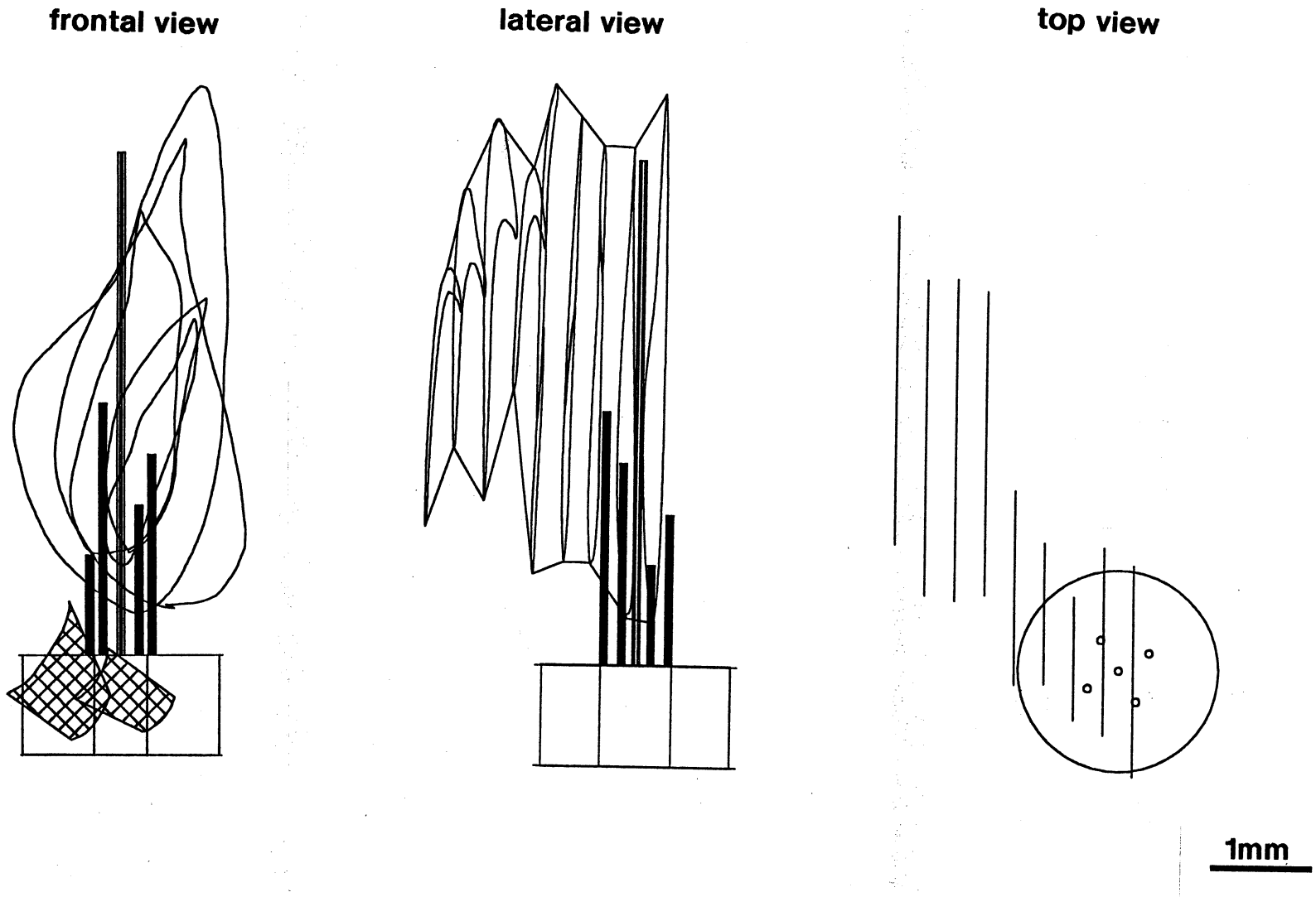

Fig 6. 4 iridium electrodes, 1–2.5 mm

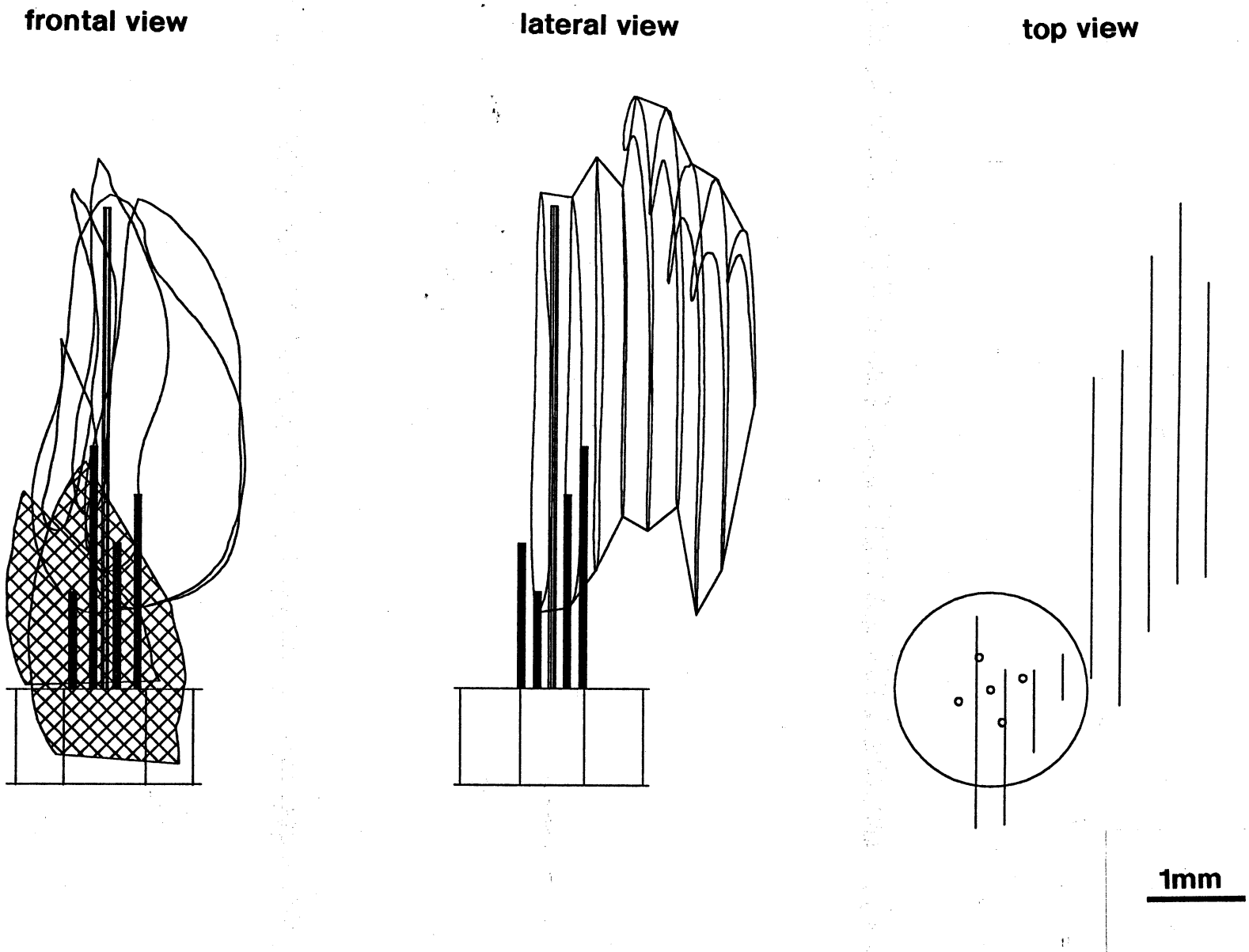

Fig 7. 4 iridium electrodes, 1–2.5 mm

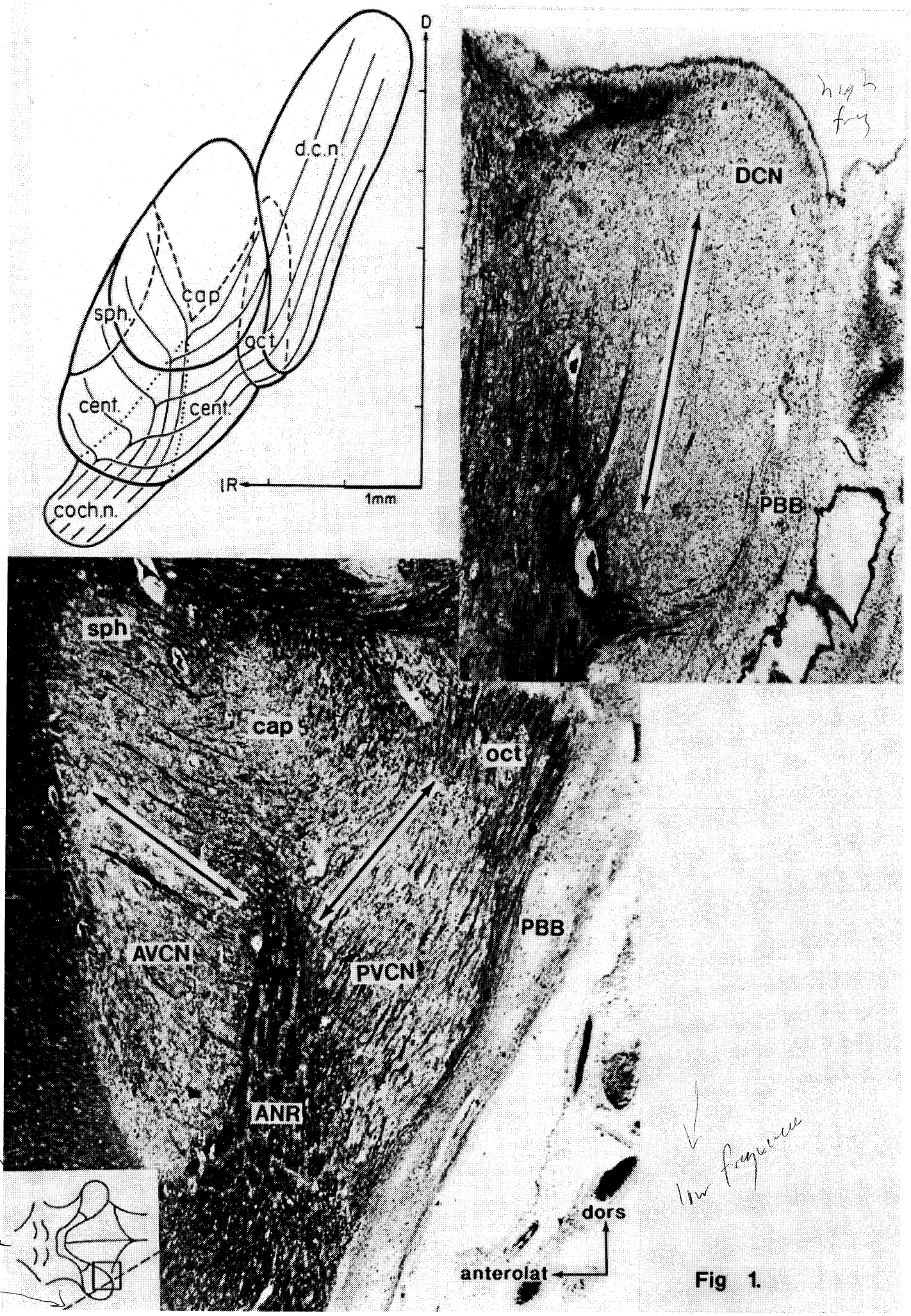
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Fig 1.