"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

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SUMMARY

I: Prolonged pulsing of microelectrodes after long-term residence in a cat's cochlear nucleus

A stimulation regimen spanning 28 days was conducted in a cat in which the microelectrode arrays had been implanted in the posteroventral cochlear nucleus for 374 days. We had 3 objectives in this study:
1.Verify that the evoked neuronal responses are stable during an extended stimulation regimen using intranuclear microelectrodes that had been implanted for more than one year.
2.Determine the extent to which the dynamic range of the neuronal response can be expanded by increasing the range of the stimulus pulse amplitude.
3.Determine if there is less stimulation-induced depression of neuronal excitability near the threshold of the neuronal response when acoustic silence is mapped to a stimulus pulse amplitude of 0 rather than to a value that is close to the threshold of the neuronal responses, as we have done in previous experiments.
Another objective of this experiments was to help to elucidate the mechanisms that are responsible for stimulation-induced depression of neuronal excitability.

Two of the microelectrodes in the PVCN were pulsed for 7 hours per day on 29 successive days. The stimulus was charge-balanced cathodic-first pulse pairs, of 40 μs per phase. The pulsing rate was 250 Hz per electrode, and the electrodes were pulsed sequentially (interleaved). For these stimulation regimens, we have simulated an acoustic environment based on a computer-generated artificial voice that reproduces many of the characteristics of real speech. The artificial voice signal is logarithmically compressed and then sets the amplitude of the charge-balanced stimulus pulses. The artificial voice signal was presented for 15 seconds, followed by 15 seconds in which the stimulus amplitude was held near the threshold of the evoked response (14 μA with a stimulus pulse duration of 40 μs/phase) or else at 0 μA. The 50% duty cycle is intended to simulate a moderately noisy acoustic environment. The cat received the regimen of stimulation outlined below:

Days	*Range of pulse amplitudes (*)*	*Silence mapped to: (~)*
1-9	14-48 μA	0 μA
10-16	14-63 μA	0 μA
17-23	14-63 μA	14 μA
24-28	14-63 μA	0 μA

(*) As generated by the logarithmically-compressed artificial voice signal
(~) Also includes 15 of every 30 seconds, according to the 50% duty cycle of the AVS

The dynamic range of the neuronal response evoked by the intraneural microstimulation was slightly greater when the maximum stimulus amplitude was increased to 63 μA, in spite of slightly more depression of neuronal excitability. Also, the total dynamic range of the neuronal response may be slightly greater if (near) silence is represented by a stimulus pulse amplitude of 0 μA rather than by a pulse amplitude that is close to the typical threshold of neuronal responses (e.g., 14 μA). However, it appears that only a slight advantage is to be gained by the discontinuous mapping procedure, and only those microelectrodes for which the threshold of the neuronal response initially was lower than the low end of the stimulus range would be affected (e.g., Electrode #2). Even here, only the extreme low end of the response range was affected. We have shown previously that persisting stimulation-induced depression of neuronal excitability, as revealed by a persisting shift in the non-embedded response growth function, is linked closely to the excitation of the neurons of the ventral cochlear nucleus (McCreery et al, 1997). The present results indicate that this also is true for the dynamic component of the depression, as revealed by a shift in the embedded RFG.

II: Histologic evaluation of microelectrode arrays sized for the human cochlear nucleus.

We used the hand held inserter tool to implant 2 arrays of microelectrodes into the feline cerebral cortex. The lengths of the electrodes were selected to span most of the tonotopic gradient of the human cochlear nucleus. We had two objectives in this study:

1.Continue our evaluation of the histologic effects of using the hand-held array inserter tool to implant blunt-tipped microelectrodes into a very vascular part of the brain. We are particularly inserted in the occurrence of any space-occupying microhemorrhages and microhematomas.

2.Continue our study of the relation between the duration of the implant and in the thickness of the capsule of connective tissue that forms on the underside of the electrode's superstructure. The thickness of this capsule will affect the location of the microelectrodes' tips along the tonotopic gradient of the human cochlear nucleus

The arrays had been implanted for 67 days, but the capsules on the underside of both of their superstructure were approximately 150 µm in thickness, in fact slightly less than those on the underside of the arrays that have been implanted for approximately 30 days (QPR #6). This suggests that the growth of these capsules is either very slow or is self-limiting.

We examined the tracks of 16 microelectrodes and stabilizing pins ranging in length from 1 to 3 mm. As in previous animals, gliotic scars always surrounded the tips of the longest microelectrodes. There was minimal scarring around the tips of the shortest (1 mm) electrodes and slightly more scarring adjacent to the tips of electrode of intermediate length, with normal- appearing neurons within 25 to 50 µm of the tip site. To date, 40 electrode tracks from 6 such arrays have been examined, and we have found little evidence of new or resolved hemorrhages (erythrocytes or hemosiderin). This speaks well for the safety of implanting the arrays using the hand- held inserter tool.

I: Prolonged pulsing of microelectrodes after long-term residence in a cat's cochlear nucleus

A stimulation regimen spanning 28 days was conducted in a cat in which the microelectrode arrays had been implanted in the posteroventral cochlear nucleus for 374 days. We had 3 objectives in this study:
1.Verify that the evoked neuronal responses are stable during an extended stimulation regimen using intranuclear microelectrodes that had been implanted for more than one year.
2.Determine the extent to which the dynamic range of the neuronal response can be expanded by increasing the range of the stimulus pulse amplitude.
3.Determine if there is less stimulation-induced depression of neuronal excitability near the threshold of the neuronal response when acoustic silence is mapped to a stimulus pulse amplitude of 0 rather than to a value that is close to the threshold of the neuronal responses, as we have done in previous experiments. Many of the sound processors now used in cochlear implants are able to map sound amplitude (pressure) to stimulus pulse amplitude according to an arbitrary power function. These processors can implement a discontinuous mapping function so that sound pressure less than an arbitrarily defined value can be mapped to a stimulus pulse amplitude of 0 μA. Another objective of this experiments was to help to elucidate the mechanisms that are responsible for stimulation-induced depression of neuronal excitability.

METHODS

Iridium stimulating microelectrodes with blunt tips (radius of curvature of 5 to 6 μm) were fabricated from lengths of pure iridium wire 70 μm in diameter. The entire shaft and wire junction is coated with 3 thin layers of Epoxylite 6001-50 heat-cured electrode varnish. The insulation was removed from the tip with an excimer laser, leaving an exposed geometric surface area of 2000 +/- 400 μm^2. The individual electrodes were assembled into an integrated array of microelectrodes spaced approximately 400 μm apart. The iridium electrodes were "activated" to increase their charge capacities. They were cleaned, soaked in deionized water for 24 hours, and sterilized with ethylene oxide.

Using general anesthesia and aseptic technique a pair of stainless steel recording electrodes was implanted by stereotaxis into the right inferior colliculus through a small craniectomy. The array of 3 iridium stimulating electrodes was then implanted into the left posteroventral cochlear nucleus (PVCN).

Beginning 374 days after implantation of the electrodes, two of the microelectrodes were pulsed for 7 hours per day on 29 successive days. The stimulus was charge-balanced cathodic-first pulse pairs, of 40 μs per phase. The pulsing rate was 250 Hz per electrode, and the electrodes were pulsed sequentially (interleaved). For these stimulation regimens, we have simulated an acoustic environment based on a computer-generated artificial voice that was specified and provided by the International Telegraphic & Telephony Consultive Convention, for the purpose of testing telecommunication equipment. The CCITT artificial voice reproduces many of the characteristics of real speech, including the long-term average spectrum, the short-term spectrum, the instantaneous amplitude distribution, the voiced and unvoiced structure of speech, and the syllabic envelope. The artificial voice signal is passed through a full wave rectifier and then undergoes logarithmic amplitude compression, before being sent through an appropriate anti-aliasing filter. The amplitude of the signal from the filter then sets the amplitude of the charge-balanced stimulus pulses. The artificial voice signal was presented for 15 seconds, followed by 15 seconds in which the stimulus amplitude was held near the threshold of the evoked response (14 μA with a stimulus pulse duration of 40 μs/phase) or else 0 μA. This 50% duty cycle is intended to simulate a moderately noisy acoustic environment. During the 7 hours of daily stimulation, the range of pulse amplitudes generated by the artificial voice signal was shifted so as to range for 14 to 48 or else 14 to 63 μA. Acoustic silence (including the 15 seconds during the OFF phase of the duty cycle) was mapped to a pulse amplitude of either 14 μA (close to the threshold of the neuronal response recorded in the central nucleus of the inferior colliculus while stimulating in the PVCN) or to 0 μA.

Figure 1 shows an averaged evoked response (AER) recorded in the inferior colliculus while stimulating with one of the microelectrodes in the contralateral posteroventral cochlear nucleus. The amplitude of the first and second components of the AER was measured from the peak of the positivity to the trough of the subsequent negativity . Because of its short (~ 1 ms) latency after the stimulus, the

early component is assumed to represent neuronal activity evoked directly in the neurons projecting from the PVCN to the inferior colliculus, while the second component may represent neuronal activity that is evoked transsynaptically. All of the response growth functions described in this report were generated from the first component. The threshold of the evoked response is typically 14 +/- 2 μA when the stimulus pulse duration is 40 μs/phase.

The response growth functions, which represent the recruitment of the neural elements surrounding the microelectrode, were generated for individual stimulating microelectrode by plotting the amplitude of the first component of each of the microelectrode's AERs against the amplitude of the stimulus that evoked the AER. The "non-embedded" RGFs were generated before, and also immediately after the daily 7-hour sessions of stimulation. They were generated using a 50 Hz "probe" stimulus (a much lower frequency than the 250 Hz used during the 7-hour stimulation session). They are designated "non-embedded response growth functions" since they were not acquired during the 7-hour session, and thus not contemporaneously with the artificial voice signal,

"Embedded" response growth functions also were acquired during the last hour of each of the 7-hour sessions, while stimulating with the artificial voice signal, and at the full rate of 250 Hz per electrode. At least 35 minutes are required to generate each of the embedded response growth functions. The procedure by which they are acquired is described in McCreery et al, (2000) and in previous quarterly reports.

The non-embedded response growth functions reveal depression of neuronal excitability (SIDNE) that persists long after the end of the 7 hours of high-rate stimulation with the artificial voice signal, and may help to identify stimulation protocols that place inordinate stress on the neurons of the ventral cochlear nucleus. The embedded growth functions reveal how the regimen of prolonged stimulation affects the neurons' responses to the actual artificial voice signal. The non-embedded and embedded responses, and the histologic evaluation of the implant sites, together provide a picture of the safety and efficacy of the stimulation regimen.

The stimulation and data acquisition was conducted using a two-way radiotelemetry stimulation and data acquisition system, and the cats are able to move about freely in a large Lucite cage.

The cat (CN-139) received the regimen of stimulation outlined in table I. She was stimulated for 7 hours per day using a 50% duty cycle (15 seconds of stimulation and 15 seconds without stimulation with the artificial voice signal).

Table I

Days	**Range of pulse amplitudes (*)**	**Silence mapped to: (~)**
1-9	14-48 μA	0 μA
10-16	14-63 μA	0 μA
17-23	14-63 μA	14 μA
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(*) As generated by the logarithmically-compressed artificial voice signal
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The RGFs evoked while stimulating in the PVCN with microelectrode #1 or #2 are shown in Figure 2 and 3, respectively. The 28-day regimen began with the pulse amplitudes modulated between 14 and 48 μA and with acoustic silence was mapped to 0 μA. Figure 2A and 3A show the pre-stimulus (reference) non-embedded RGFs. Figure 2A and 3A also show the non-embedded and embedded RGFs at the end of the 9th day and also the 10th day, when the range of the stimulus amplitude was increased to 14 to 63 μA. As in previous experiments, the non-embedded RGF shifted downwards when the upper end of the stimulus range was increased, indicating more stimulation-induced depression of neuronal excitability (SIDNE). The embedded RGF's also shifted downwards slightly (compare curves e9 and e10), but the dynamic range of the neuronal responses was slightly greater nonetheless. This small expansion of the dynamic range persisted through Day 16 (Figure 2B, 3B). On Day 17, the protocol was altered so that acoustic silence was mapped to a stimulus amplitude of 14 μA, which is close to the threshold of the

neuronal responses (Figure 2C, 3C). The embedded response evoked from microelectrode #1 was essentially unaffected by this change (figure 2C) , but the threshold of the embedded response evoked from Electrode #2 (Figure 3C) did increase slightly. The embedded RGF was essentially unaffected at the upper end of its range. On the 24th day, the protocol again was changed so that acoustic silence again was again mapped to 0 μA (Figure 2D, 3D). The threshold of the embedded RGF from Electrode #2 decreased, and at the end of the 28th day, the embedded RGFs from both electrodes were very similar to the RGFs at the end of the 10th day (the first day in which the range of stimulus amplitudes was expanded to 14-63 μA).

In summary, the dynamic range of the neuronal response evoked by the intraneural microstimulation was slightly greater when the maximum stimulus amplitude was increased to 63 μA, in spite of slightly more depression of neuronal excitability. Also, the total dynamic range of the neuronal response may be slightly greater if (near) silence is represented by a stimulus pulse amplitude of 0 μA rather than by a pulse amplitude that is close to the typical threshold of neuronal responses (e.g., 14 μA). However, it appears that only a slight advantage is to be gained by the discontinuous mapping procedure, and only those microelectrodes for which the threshold of the neuronal response initially was lower than the low end of the stimulus range would be affected (e.g., Electrode #2). Even here, only the extreme low end of the response range is affected. We have shown previously that persisting stimulation-induced depression of neuronal excitability, as revealed by a persisting shift in the non-embedded response growth function, is linked closely to the excitation of the neurons of the ventral cochlear nucleus (McCreery et al, 1997). The present results indicate that this also is true for the dynamic component of the depression, as revealed by a shift in the embedded RFG.

II: Histologic evaluation of microelectrode arrays sized for the human cochlear nucleus.

INTRODUCTION

We used the hand held inserter tool to implant 2 arrays of microelectrodes into the feline cerebral cortex. The lengths of the electrodes were selected to span most of the tonotopic gradient of the human cochlear nucleus. We had two objectives in this study:

1.Continue our evaluation of the histologic effects of using the hand-held array inserter tool to implant blunt-tipped microelectrodes into a very vascular part of the brain. We are particularly inserted in the occurrence of any space occupying microhemorrhages and microhematomas.

2.Continue our study of the relation between the duration of the implant and in the thickness of the capsule of connective tissue that forms on the underside of the electrode's superstructure. The thickness of this capsule will affect the location of the microelectrodes' tips along the tonotopic gradient of the human cochlear nucleus.

The feline ventral cochlear nucleus contains cell types that are very similar to those in the human VCN, but it is not a good site in which to evaluate the human array and the inserter tool, due to its shape and location as a pendulous structure on the dorsolateral surface of the brainstem. We have therefore implanted the human-type cochlear nucleus arrays into the feline lumbar spinal cord and also into the cerebral cortex (QPR#6). For this type of evaluation, the spinal cord is probably the best feline model for the human auditory brainstem, but one difference is that it is covered by dura rather than by the lateral cerebellum, as is the human auditory brainstem (cats have only a small subarachnoid space over their lumbar enlargement). The second site, the feline cerebral cortex, allows us to evaluate the arrays when they are implanted into very vascular brain tissue. Also, the cortical gray matter spans nearly the same range of depths beneath the pia as does the human ventral cn.

METHODS

Arrays of stimulating microelectrodes were fabricated from sections of iridium wire 50 μm in diameter. The tips of the microelectrodes were shaped electrolytically to a rather blunt point, with a radius

of curvature of 6 ± 1µm. The electrodes were coated with Epoxylite electrode varnish which was removed from the tip with the aid of an excimer laser. Figure 4 shows an electrode array. This particular example has 4 working electrodes and 2 stabilizing pins. All 6 pins extend downwards from an epoxy button superstructure which is 2.5 mm in diameter. This array is designed to be implanted into the ventral cochlear nucleus with the aid of a hand-held instrument, which has been described previously. The arrays implanted into cat CNH15 had 6 working electrodes ranging, in length from 1 to 2 mm (in order to span the full dorsoventral extent of the human ventral cochlear nucleus, when the electrodes are inserted through the taenia choroidea), and a pair of 3.2 mm stabilizer pins, whose tips are identical to those of the 6 working electrodes, but are not insulated.

Using general anesthesia and aseptic technique, a craniectomy was made over the parietal cortex. Just prior to loading the array into the inserter tool, the arrays and the barrel of the tool were sonicated for 3 minutes in 100% ethanol and then for 1 minute in sterile water. The two array was inserted at a velocity of approximately 1m/sec. The dura flat was then pulled back over the arrays and covered with a patch of fascia resected from the temporalis muscle. The muscle layers and scalp were closed in layers.

None of the electrodes were pulsed. Sixty-seven days after implantation, the cat was deeply anesthetized with Pentobarbital and perfused through the aorta with ½-strength Karnvosky's fixative. The electrode arrays were removed from the brain, and blocks of cortex containing the array tracks were embedded into paraffin and sectioned at 8 µA, approximately parallel to the electrode tracks. The sections were stained with Nissl stain.

RESULTS

All 16 electrode tracts from the two arrays were located and examined. Overall, the results were very similar to those from previous animals in which the arrays had been implanted for 30 to 34 days (QPR #6).

Figure 5A shows a histologic section through the track of one of the short (1.2 mm) microelectrodes from the caudal array. The section is nearly in the plane of the electrode shaft and the pear-shaped distortion of the track is an artifact that occurred after the histologic section was cut. The electrode tip (T) was approximately 950 µm below the pia which has been compressed slightly by the underside of the array superstructure. The electrode track is surrounded by a very thin glial sheath with normal-appearing neurons within 25-50 µm of the tip site. The narrow glial scar extending downward below the tip site probably was formed as the array was shimmed upwards by the growth of the connective tissue capsule on the underside of the superstructure. A remnant of the capsule itself can be seen at the top of the photograph. It is approximately 150 µm in thickness. The capsule on the underside of the caudal array was similar. These arrays has been implanted for 67 days, but the capsules were slightly thinner than those on the underside of the arrays that have been implanted for approximately 30 days (QPR #6). This suggests that the growth of these capsules is either very slow or is self-limiting.

Figure 5B and 5C show the tip sites of 2 other short electrodes from the caudal and rostral array, respectively. There was virtually no scarring adjacent to the shafts and tips of any of the 4 short (1 mm) microelectrodes. As in previous animals, the scarring was slightly greater near the tips of the longer microelectrodes. Thus, figure 5D, E and F show the tip sites of 2 microelectrodes, which were located 1,500 µm beneath the pia. The asymmetric gliotic scar (S) in Figure 5E is unusually large (approximately 125 µm in width) for an electrode of this lenght. The shape of the scar indicates that it may be a healed microhemorrhage, although the absence of hemosiderin does argue against this origin. Hemosiderin forms rusty-brown deposits which when present are easily visible against the blue Nissl stain.

Figures 5G and 5H show the tip sites of 2 of the stabilizer pins whose tips were in the white matter at a depth of 2,800 and 2,850 µm. As in previous animals, the scarring (S) was more severe near the tips of these very long shafts. Also, as in previous animals, the scarring was greatest just above the tips. There were glial scars located a few hundred µm above the tip sites of all 4 stabilizing pins, and only thickened glial sheaths directly beneath the actual tip sites. The mechanisms that are responsible for this pattern of scarring are unknown, but we have speculated that it is due to repetitive movement of the lower

end of the electrode shafts relative to the surrounding tissue. We would expect that when the superstructure floats on the surface of the brain, which is deformable, the relative movement between electrodes and tissue would be greater near tips of the longest shafts.

DISCUSSION

Our primary motive for implanting the human-type cochlear nucleus arrays into the feline cerebral cortex is to evaluate the potential for interstitial hemorrhage when the inserter tools is used to implant the electrodes into a very vascular region of the brain. We reported that gliotic scars always surrounded the tips of the longest microelectrodes. To date, 40 electrode tracks from 6 such arrays have been examined, and we have found little evidence of new or resolved hemorrhages (erythrocytes or hemosiderin). In cat CNH7, a few very small aggregates of hemosiderin were observed near 3 or 4 of the cortical capillaries, 30 days after implanting the arrays, but no evidence of space-occupying microhemorrhages. No hemosiderin or erythrocytes was observed in any of the histologic sections from cat CNH12 or CNH15. Figure 5E shows the only one of the 40 tracks in which the asymmetric shape of the glia scar suggests that it may have originated from a healed microhemorrhage, and in this case the scar is small and is surround by normal-appearing tissue. These findings speaks well for the safety of implanting the arrays using the hand held tool.

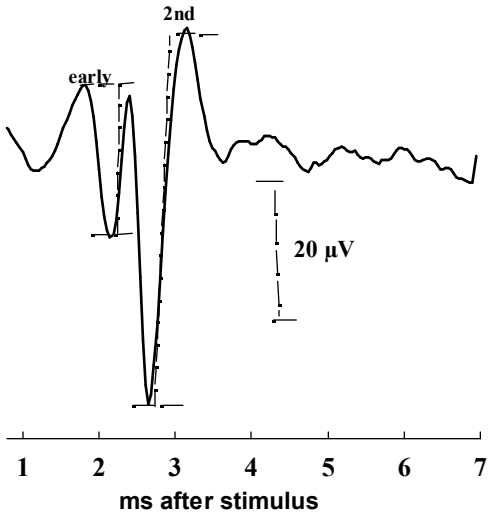
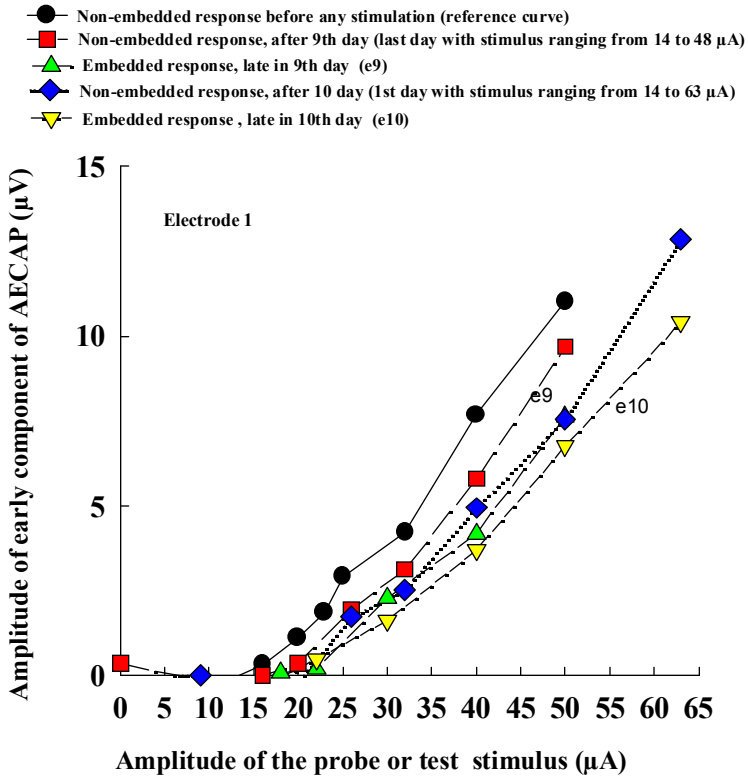


Figure 1

A



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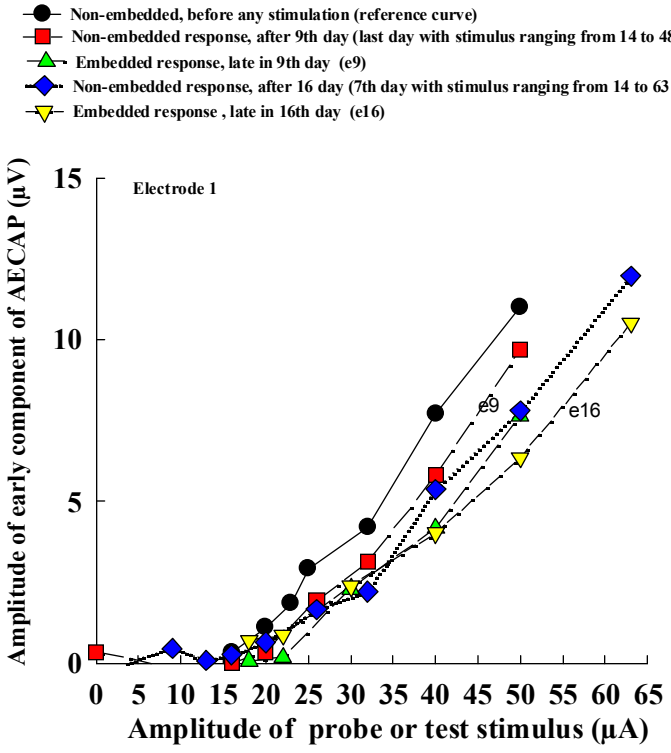

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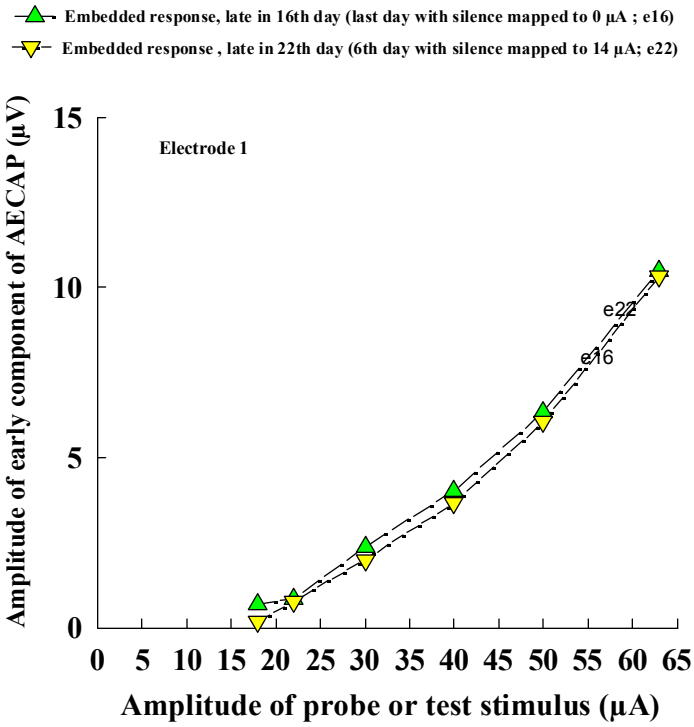
Figure 2

C



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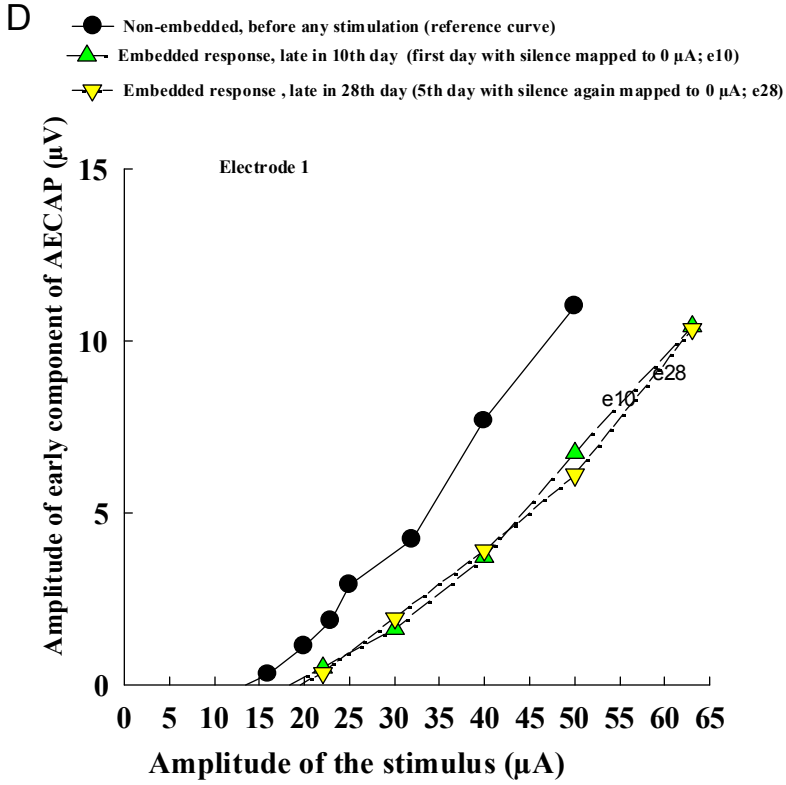

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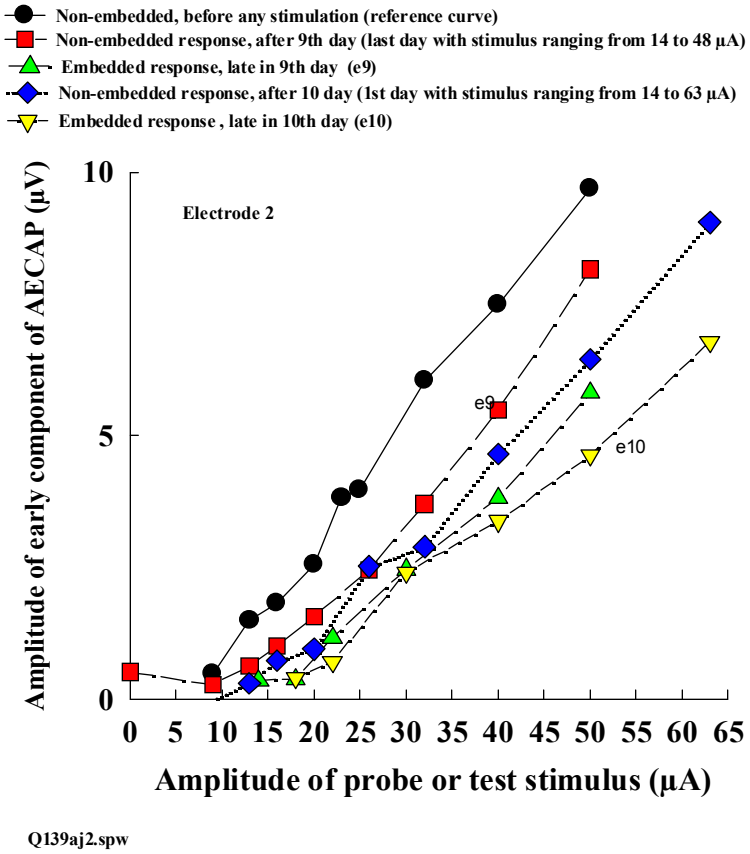
A



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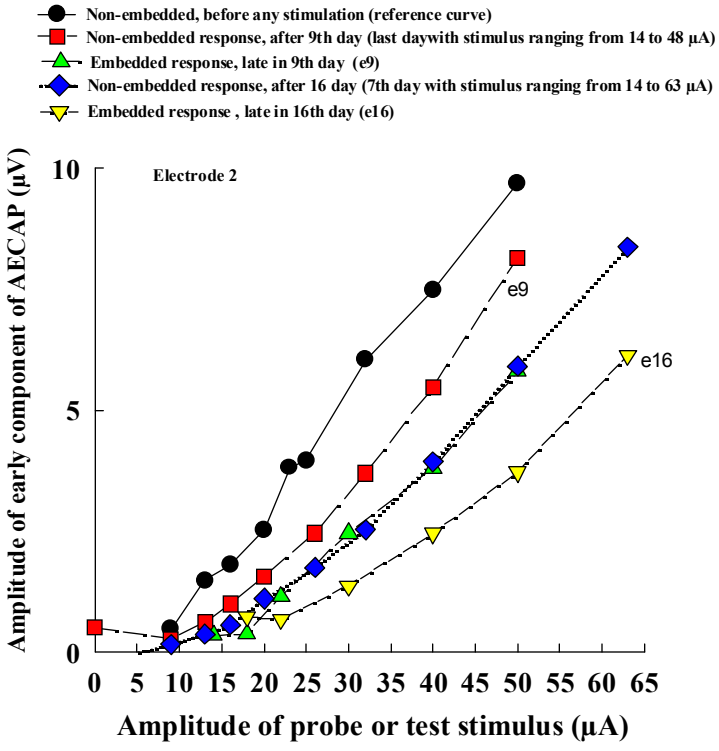

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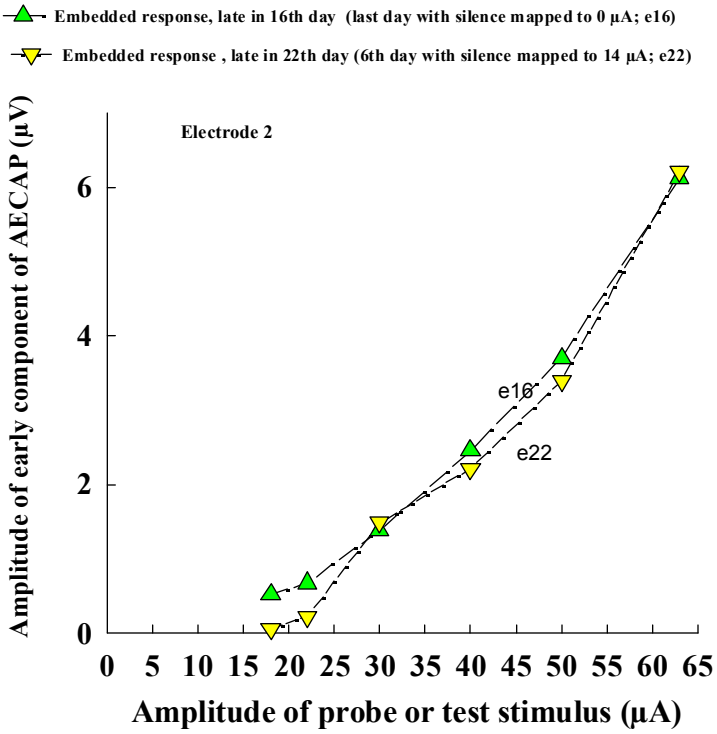
Figure 3

C



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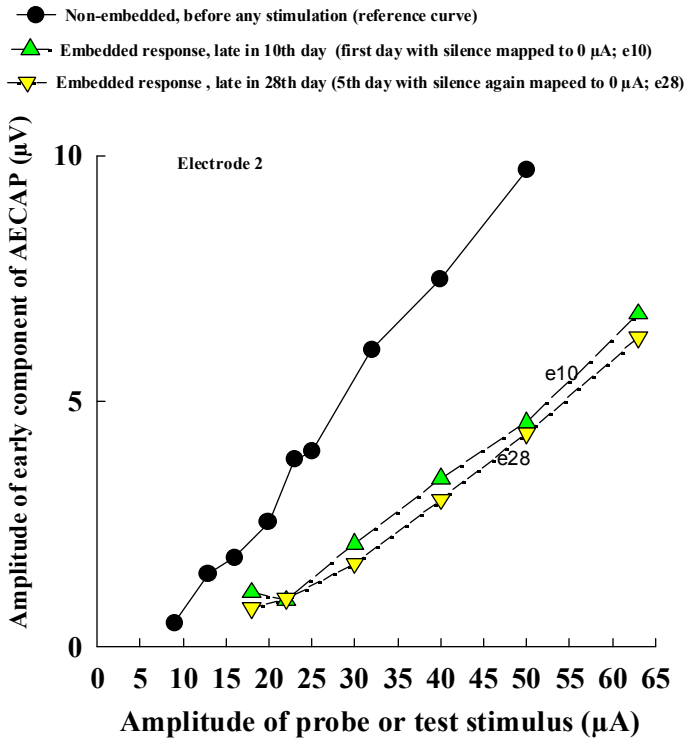

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Figure 3

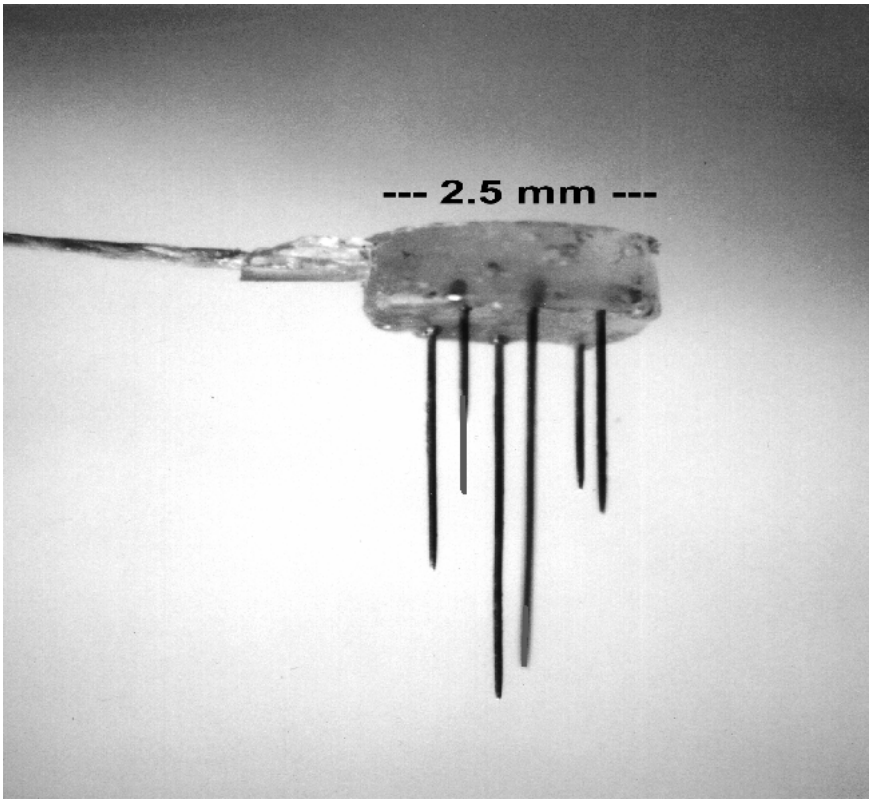

Figure 4

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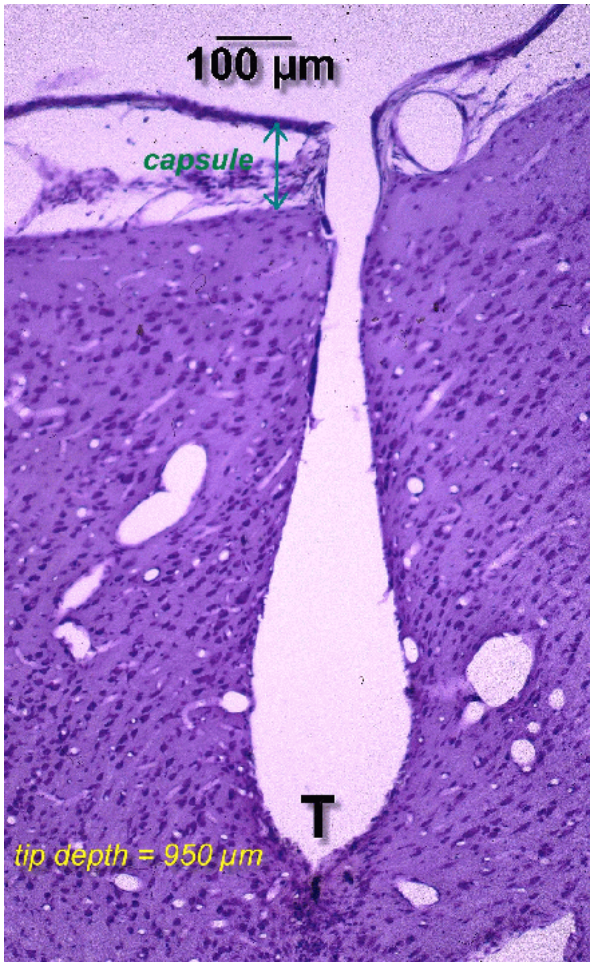

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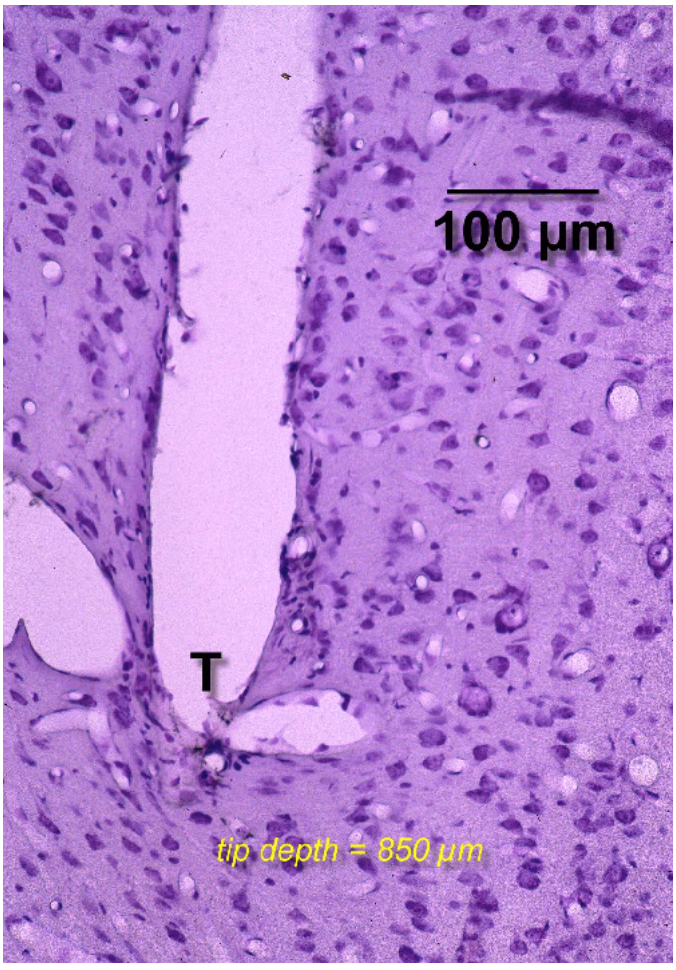
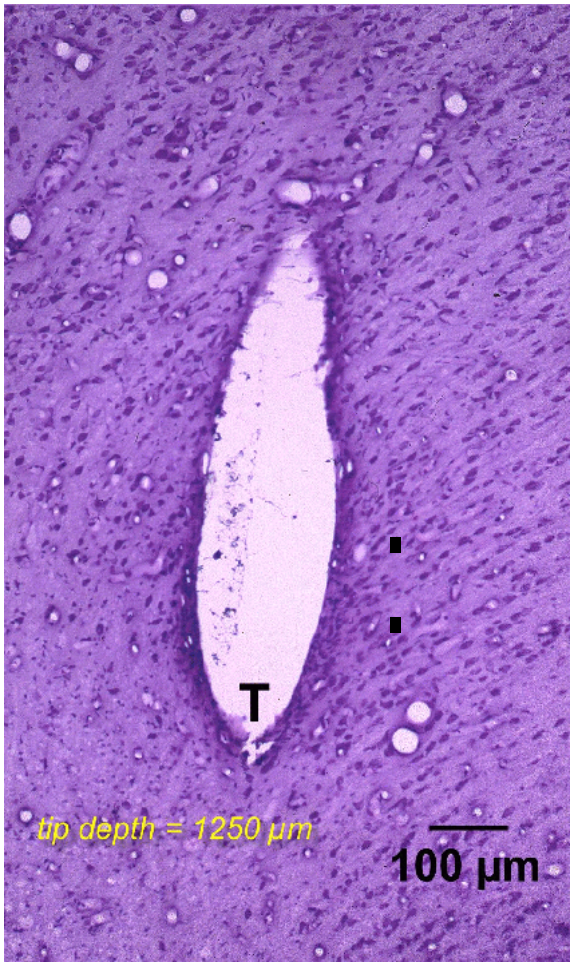


Figure 5

C



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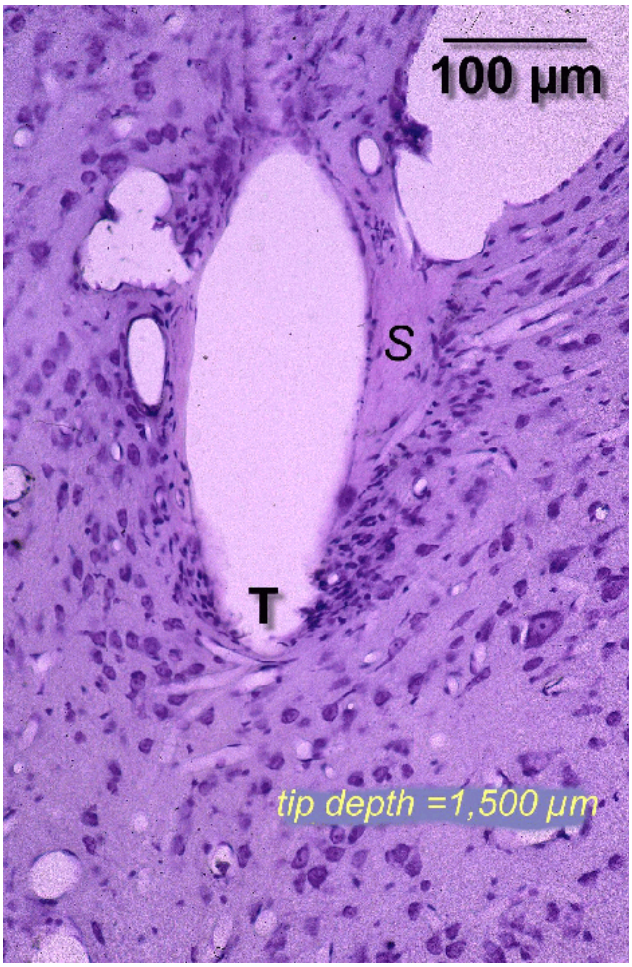

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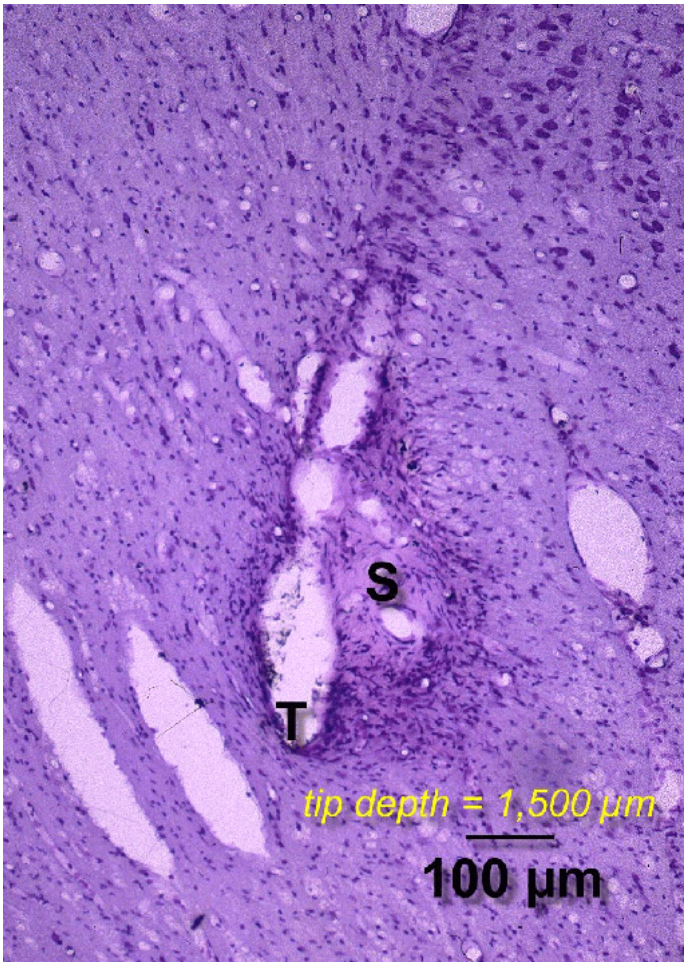

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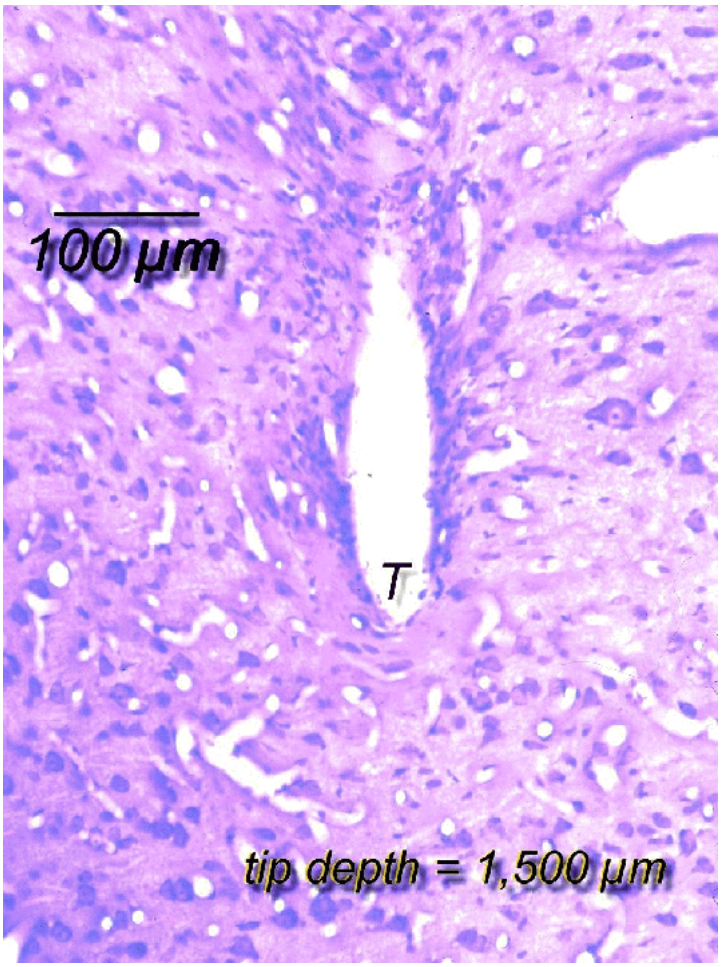

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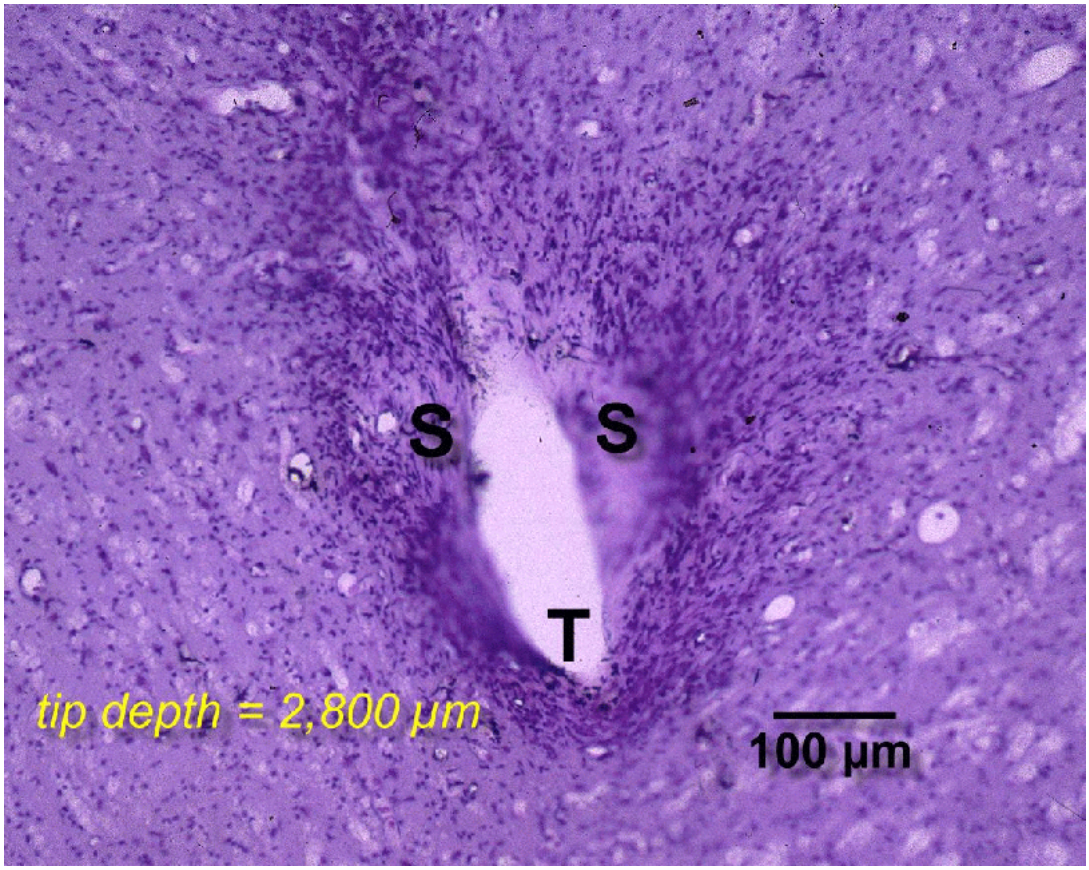
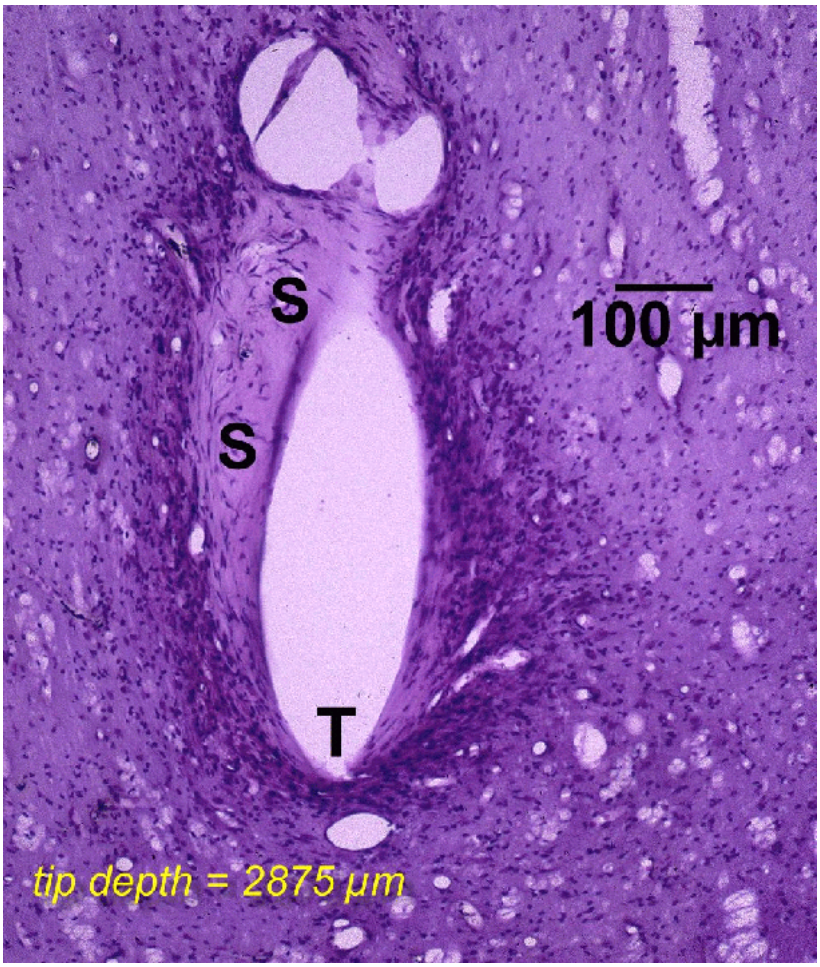


H



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