"The Feasibility of a Cochlear Nucleus Auditory prosthesis based on microstimulation"

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ABSTRACT AND SUMMARY

These studies are a continuation of our program to determine safe and effective stimulus parameters for an auditory prosthesis based on multisite microstimulation in the ventral cochlear nucleus. Arrays of three discrete iridium microelectrodes were implanted into the posteroventral cochlear nucleus of adult cats. Beginning 75 to 240 days after implantation, two of the microelectrodes were pulsed for 7 hours per day on 15 successive days, using biphasic current pulses whose amplitude was modulated according to a logarithmically-compressed artificial voice signal. Each microelectrode was pulsed at 250 Hz, and the stimulus was interleaved between the microelectrodes.

The electrical excitability of the neurons near the stimulating microelectrodes was assessed from the changes in the recruitment characteristics of the compound evoked response recorded in the contralateral inferior colliculus. When the range of the artificial voice signal was 6 to 32 μA (0.9 to 4.8 nC/phase), marked depression of neuronal excitability developed during the prolonged stimulation, and most of the depression developed during the first 7-hour session of stimulation. The depression was detected when the recruitment curves were generated from low-frequency pulsing after each of the 7-hour sessions, and also when the curves were generated during (near the end) of the 7-hour sessions of stimulation with the artificial voice signal. These "non-embedded" and "embedded" recruitment curves each provide their own insights into the effects of the prolonged stimulation.

Although there was marked depression of neuronal excitability, histological evaluations of the electrodes sites did not reveal any tissue injury attributable to the prolonged electrical stimulation. This implies that the depression of neuronal excitability would eventually disappear.

INTRODUCTION

Previous work in our laboratory has shown that histologically-detectable tissue

injury will occur in the feline posteroventral cochlear nucleus when the individual microelectrodes are pulsed continuously for 7 hours at 500 Hz, and the charge per phase exceeds 3 nC (20 μA with a pulse duration of 150 μsec/phase), (McCreery et al, 1994). Our recent studies of the efficacy and safety of microstimulation in the cat PVCN has used interleaved pulse trains modulated according to a logarithmically-compressed artificial voice signal. The distribution of pulse amplitudes, as determined by the logarithmically compressed artificial voice signal, is shown in Figure 1. The range of the pulse amplitudes has been shifted and adjusted so that the lowest stimulus amplitude (corresponding to acoustic silence) is represented by a pulse amplitude of 6 μA, and at the high end of the scale, 98% of the pulses have amplitudes less than 20 μA. The signal is clipped at 20 μA. The second peak at the high end of the amplitude scale is due to the logarithmic amplitude compression, which forces the entire upper end of the signal's amplitude range into a small portion of the pulse amplitude range. However, even with this transformation, high-amplitude pulses will occur relatively infrequently, and nearly half will have pulse amplitudes less than 15 μA. Therefore, we examined the physiologic and histologic effects of stimulating for 7 hours/day on 15 consecutive days using a pulse train modulating according to the artificial voice signal in which the range of pulse amplitudes is 6 to 32 μA, at 250 Hz per electrode, with the hope and expectation that the high amplitude pulses would be relatively innocuous because they occur at a relatively low average frequency.

METHODS

Fabrication of stimulating microelectrodes.

Activated iridium stimulating microelectrodes are fabricated from lengths of pure iridium wire, 50 μm in diameter. A Teflon-insulated lead wire is welded to one end of the iridium shaft, and the other end was shaped to a conical taper, by electrolytic etching. The microelectrodes have relatively blunt tips (a radius of curvature of approximately 6 μm) to reduce tissue injury during insertion into the brain. The entire shaft and wire junction then is coated with 3 thin layers of Epoxylite 6001-50 heat-

cured electrode varnish. The insulation is removed from the tip by dielectric destruction. leaving an exposed geometric surface area of approximately 1000 μm^2. The individual electrodes are assembled into an integrated array of 3 or 4 microelectrodes spaced 400 μm apart. The integrated array, with its closely-spaced microelectrode shafts, is designed to approximate the dimensions of an array that can be implanted into the human posteroventral cochlear nucleus using a tool inserted through the translabyrinthine surgical approach to the CP angle. The shafts of the electrodes extend 4 mm beyond the array's superstructure. Electrodes 4 to 5 mm in length will be required to reach all the way through the human ventral cochlear nucleus.

The iridium electrodes are then "activated" to increase their charge capacities, soaked in deionized water for 120 hours, and sterilized with ethylene oxide.

Implantation of stimulating and recording electrodes

Young adult cats were anesthetized with Pentothal sodium, with transition to a mixture of nitrous oxide and Halothane. Implantation of the electrodes was conducted using aseptic surgical technique. The cat's head was placed in a stereotaxic frame, and the skull was exposed as far back as the posterior fossa by reflecting the scalp and muscles. A pair of stainless steel recording electrodes was implanted by stereotaxis into the right inferior colliculus through a small craniectomy. The deeper electrode was positioned just below the central nucleus of the colliculus, and the upper electrode was placed dorsal to the surface of the colliculus. The compound action potential induced by a train of clicks delivered to the left ear was used to position the recording electrodes. The introducers surrounding the electrodes were then retracted and the shafts of the electrodes were cemented to the skull by flooding the small craniectomy with methylmethacrylate.

A small craniectomy was made in the posterior fossa over the cerebellum, through which the array of iridium stimulating electrodes was inserted by stereotaxis into the left posteroventral cochlear nucleus (pvcn). Since the feline cochlear nucleus lies on the lateral surface of the brainstem and the human cochlear nucleus is buried

behind the middle cerebellar peduncle, the feline array of 4 mm microelectrodes was inserted through a portion of the overlying cerebellar flocculus, so that we could evaluate electrodes whose length was appropriate for use in humans. The microelectrodes were positioned first by stereotaxic coordinates and the final positioning was achieved by observing the compound potential evoked in the inferior colliculus while stimulating with the microelectrode.

Stimulation protocols and data acquisition

For the prolonged stimulation regimen, we have simulated an acoustic environment with a computer-generated artificial voice The 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 then 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 which are delivered to each electrode at 250 Hz, in an interleaved manner. The range of spike amplitudes is shifted so that acoustic silence is represented by a stimulus amplitude of 6 μA, which is close to the response threshold of the neurons near the tip of the properly functioning microelectrodes. The maximum amplitude of the stimulus pulses was set either to 20 or to 32 μA. Figure 1 shows the distribution of amplitudes of the stimulus pulses, when the range is 6 to 20 μA. The artificial voice signal was presented for 15 seconds followed by 15 seconds in which the stimulus amplitude was held at 6 μA which is near the threshold of the evoked response. This 50% duty cycle is intended to simulate a moderately noisy acoustic environment. The electrical stimulation was administered for 7 hours per day, on 15 consecutive days. Stimulation and data acquisition was conducted using the two-way radiotelemetry stimulation and data acquisition system described previously (QPR # 4, Contract NO1-NS-2-2323). This telemetry system and its companion software allows

continuous monitoring of the voltage waveform across the stimulating microelectrodes, and of the compound evoked potential induced in the inferior colliculus by the stimulating microelectrodes.

At intervals after implantation, and before and after each daily session of stimulation, the recruitment curves of the evoked responses were recorded in the inferior colliculus. The responses evoked by 1024 to 4096 consecutive charge-balanced, controlled-current stimulus pulses applied to the stimulating microelectrodes were averaged to obtain an averaged evoked compound action potential (AECAP). For each AECAP, the amplitude of the first or second component was measured after the averaged response is filtered through a low-pass filter with a bandwidth of 250 Hz to 2.5 kHz. The amplitude of the early and second components is measured from the peak of the positivity on the leading edge to the trough of the subsequent negativity. The response growth function (recruitment curve), which representing the recruitment of the excitable neural elements surrounding the microelectrode, is generated by plotting the amplitude of the first or second component of each of several AECAPs against the amplitude of the stimulus pulse that evoked the responses.

The conventional (non-embedded) recruitment curves were generated before and immediately after the sessions of prolonged stimulation. The stimulus frequency was 50 Hz, which is much lower than during the 7-hour test session. In addition, a limited number of "embedded" recruitment curves were acquired during the first or last 45 minutes of some of the 7-hour sessions of stimulation , during the occurrence of the 250 Hz, amplitude-modulated pulse train . This procedure, which requires approximately 45 minutes per microelectrode , was described in detail in QPR #5. Briefly, when the appropriate pulse amplitude (e.g., 6 μA) is generated by the artificial voice, subsequent stimulus pulses are suspended for 8 msec, which is long enough for the first and second components of the evoked response to be recorded in the inferior colliculus. Pulsing at the full stimulus rate then resumes, and the computer waits 100 msec before resuming its search for the next 6 μA pulse, at which time another evoked response is recorded. This is repeated until the required number of responses to 6 μA

has been collected and averaged, and the process is repeated for each of 7 stimulus amplitudes. The conventional (non-embedded) recruitment curves allow detection of depression of neuronal excitability that persists after the termination of the high-rate stimulation with the artificial voice signal. This type of depression may persist for several days if it is severe. Changes in the non-embedded recruitment curves flag stimulation protocols that place significant stress on the neurons of the lower auditory system. The embedded recruitment curves, in contrast, allows us to determine how the regimen of prolonged stimulation affects the neuronal response to the actual artificial voice signal. The non-embedded and embedded responses, and the histologic evaluation of the implant sites, together provide extensive and complementary data on the safety and efficacy of the stimulation regimen.

Histologic evaluations

Within 15 minutes after the end of the last day of stimulation, the cats were deeply anesthetized with pentobarbital and perfused through the aorta with ½ strength Karnovsky's fixative (2.5% glutaraldehyde, 2% paraformaldehyde and 0.1M sodium cacodylate buffer). The cochlear nucleus and adjacent portion of the brainstem were resected, embedded in paraffin, sectioned serially in the frontal plane (approximately parallel to the shafts of the stimulating microelectrodes) at a thickness of 8 μm, and stained with Cresol Violet (Nissl stain) or with hematoxylin and eosin.

RESULTS

CN111.

The 15-day stimulation regimen was begun 240 days after implantation of the microelectrodes into the ventral cochlear nucleus. Figure 2 shows an average evoked response from Microelectrode #1 in the left PVCN . The response was recorded in the right inferior colliculus. These microelectrodes were near the medial margin of the PVCN and there is a large fist and second component in the AECAP. Since the first component begins less than 1.2 msec after the stimulus, it probably represents neural activity evoked directly in the cochlear nucleus neurons that project through the inferior colliculus. The second component probably represents the post-synaptic excitation of neurons in the inferior colliculus.

Electrodes 1 and 3 were pulsed for 7 hours/day on each of 15 successive days. The pulses were modulated over the range of 6-32 μA according to the logarithmically-compressed artificial voice signal. The artificial voice signal was presented for 15 seconds followed by 15 seconds in which the stimulus amplitude was held at 6 μA which is near the threshold of the evoked response. This 50% duty cycle is intended to simulate a moderately noisy acoustic environment.

Figures 3A and 3B shows the non-embedded recruitment of the first component of the AECAP evoked from microelectrode #1. Figure 3B shows the corresponding embedded recruitment of the first component. Before the start of the stimulation regimen, the embedded and non-embedded recruitment curves had the same threshold (about 6 μA). After the first day (7 hours) of stimulation, the embedded and non-embedded curves were shifted well to the right of the prestimulus (control) curves. The shift in the embedded response was particularly severe, indicating that the response of cochlear nucleus neurons to electrically-encoded speech may become markedly distorted and depressed during the first 7 hours of stimulation. However, the stimulation did not become more severe during the subsequent 14 days of the long stimulation regimen. Figures 3C and 3D show essentially identical results for stimulating Microelectrode #3.

Figures 3E and 3F show the recruitment of the second (transsynaptically evoked) component of the response evoked from Microelectrode #1. The long regimen of stimulation induced similar effects on the directly-evoked and transsynaptically-evoked (first and second) components of the AECAP (Compare Figure 3A-3B with Figure 3E-3F). This indicates that the preponderance of the effect of the electrical stimulation on neuronal excitability can be attributed to depression of the electrical excitability of the neurons in the posteroventral cochlear nucleus. This is consistent with our earlier findings of the effects of prolonged stimulation when each microelectrode is pulsed at 250 Hz, described in QPR #5.

Figure 4A (97-198) shows the site of the tip (T) of microelectrode 3, close to the medial margin of the left posteroventral cochlear nucleus and near the rostral end of the posterior nucleus (Bar = 250 μm). Figure 4B (97-435) shows the site of the tip, at higher magnification (Bar = 50 μm). Figure 4C (97-437) is a section through the glial sheath just lateral to the end of the patent track, showing a cluster of normal-appearing neurons (N) about 100 μA from the tip (above and to the left of the tip of the glia sheath). In fact, none of the neurons close to the tip are hyperchromic or shrunken, and all appear essentially normal. The surrounding neuropil appears normal, and contains no edematous axon segments, which is the cardinal feature of stimulation-induced tissue injury in the cochlear nucleus (McCreery et al, 1994). Some of the neurons ventral to the tip are somewhat flattened, and this is probably a consequence of the mechanical distortion of the tissue by these rather blunt-tipped microelectrodes. Figure 4D (97-182) shows the site of the tip of the other pulsed microelectrode (microelectrode 1), located slightly rostral to microelectrode 3. Here too, the neurons and neuropil ventral to the tip are somewhat flattened and elongated but otherwise appear to be normal. It is interesting that this type of mechanical tissue distortion persisted for 240 days after implantation of the microelectrode. Figure 4D (97-184) shows the site of the tip of the unpulsed microelectrode. The glial sheath and scar dorsal to the tip is slightly more prominent and extensive than in the case of the pulsed electrodes, but the axons and neurons ventral to the tip appear essentially normal. In

summary, the tissues adjacent to pulsed and unpulsed microelectrode sites are indistinguishable, at least at the light microscope level. There is no tissue injury or inflammatory cell responses near the tip of the pulsed or unpulsed microelectrodes. The absence of tissue injury implies that the marked depression of neuronal excitability depicted in Figure 3 would eventually recover.

CN112.

The identical 15-day stimulation regimen was administered to cat CN112, 145 days after implantation of the array. Microelectrodes 2 and 3 were pulsed for 7 hours/day on 15 successive days, using the artificial voice signal modulated over the range of 6 to 32 μA, with a 50% duty cycle. Figures 5A and 5B shows the non-imbedded recruitment of the second component of the evoked response, for microelectrodes 2 and 3, respectively. (In this animal, the early component was small and could not be measured reliably.) The depression of the neuronal excitability during the stimulation regimen was even more marked than in cat CN-111, and the depression continued to worsen between the 4th and 15th day of stimulation, a phenomenon that we have not observed previously. Unfortunately, the tissue was accidentally frozen after the cat was perfused, and therefore was not available for histologic evaluation.

CN114

In the stimulation regimen administered to CN111 and Cn112, the stimulus amplitude ranged from 6 to 32 μA. We have reported previously that when the range of the artificial voice signal is limited to 6 to 20 μA and the individual electrodes are pulsed at 250 Hz, then there is very little depression of neuronal excitability in the PVCN during a regimen of prolonged stimulation. In cat CN114, the microelectrodes had been implanted into the dorsal cochlear nucleus 50 days prior to the stimulation. Two microelectrodes were pulsed for 7 hours/day for 15 days using the artificial voice signal modulated over the range of 6 to 20 μA. Figure 6 shows the recruitment of the early component of the evoked response, which was very prominent in this animal, due

to the location of the microelectrodes. The embedded response recorded near the end of the last day of stimulation is also shown. There was little change in the recruitment curves over the course of the 15-day regimen except for a small increase in the threshold of the response.

DISCUSSION

No detectable tissue injury resulted from stimulating in the PVCN for 7 hours/day on 15 consecutive days with charge-balanced current pulses, 150 μsec per phase ind duration, and modulated according to the artificial voice signal over the range of 6 to 32 μA (0.9 to 4.8 nC/phase) at 250 Hz per microelectrode . However, in the two animals studied to date, there was marked depression of the excitability of the neurons close to the microelectrodes. The depression of the response measuring during the actual stimulation with the artificial voice signal (the embedded response) indicates that there would be marked distortion and attenuation of the response to environmental and speech sounds, and that this depression would develop during the first few hours of stimulation. The absence of histologically detectable tissue injury indicates that the neurons would eventually recover from the depression (McCreery et al 1997), but there may be no advantage in pulsing the microelectrodes over this large range of amplitudes (6 to 32 μA) since pulsing over a more limited range (6 to 20 μA, 0.9 to 3 nC/phase) produces less depression of neuronal excitability and therefore preserves more of the dynamic range of the neuronal responses during regimens of prolonged stimulation.

We have noted some variability in the severity of the stimulation-induced depression during the 15-day stimulation regimens. This may be due to the electrodes being implanted into different parts of the PVCN. On the basis of the results from one cat (CN114), the neurons in the dorsal cochlear nucleus may be particularly resistant to stimulation-induced depression of excitability. Unfortunately, its anatomical projections suggest that the dorsal cochlear nucleus is not a good site for an intranuclear auditory prosthesis.

REFERENCES

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Distribution of pulse amplitude derived from Logarithmically-compressed artificial voice signal, shifted and scaled to range from 6 to 20 μA

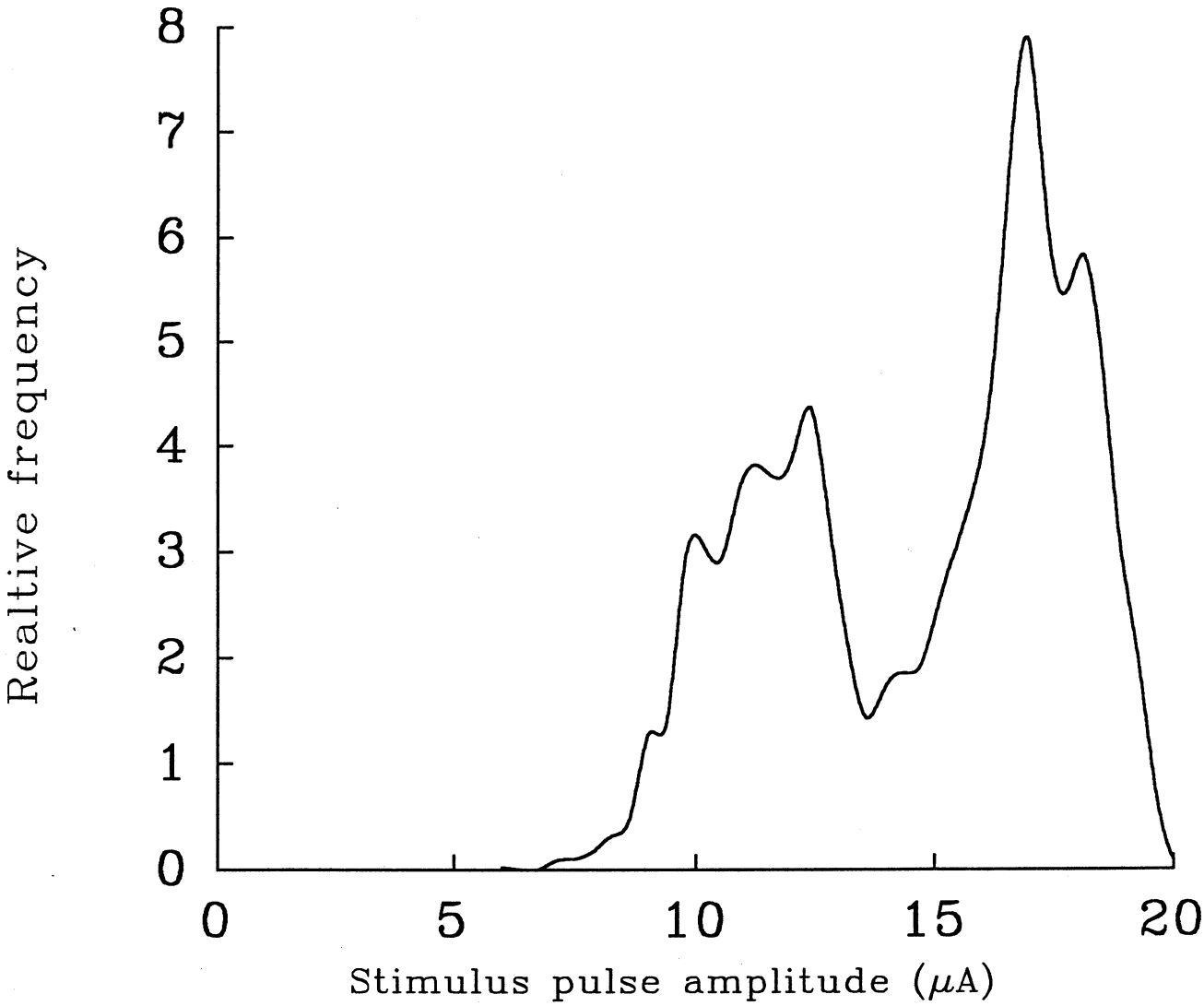

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Figure 1

cn111, electrode #1

Stimulate (16 μA) in PVCN, record in inferior colliculus

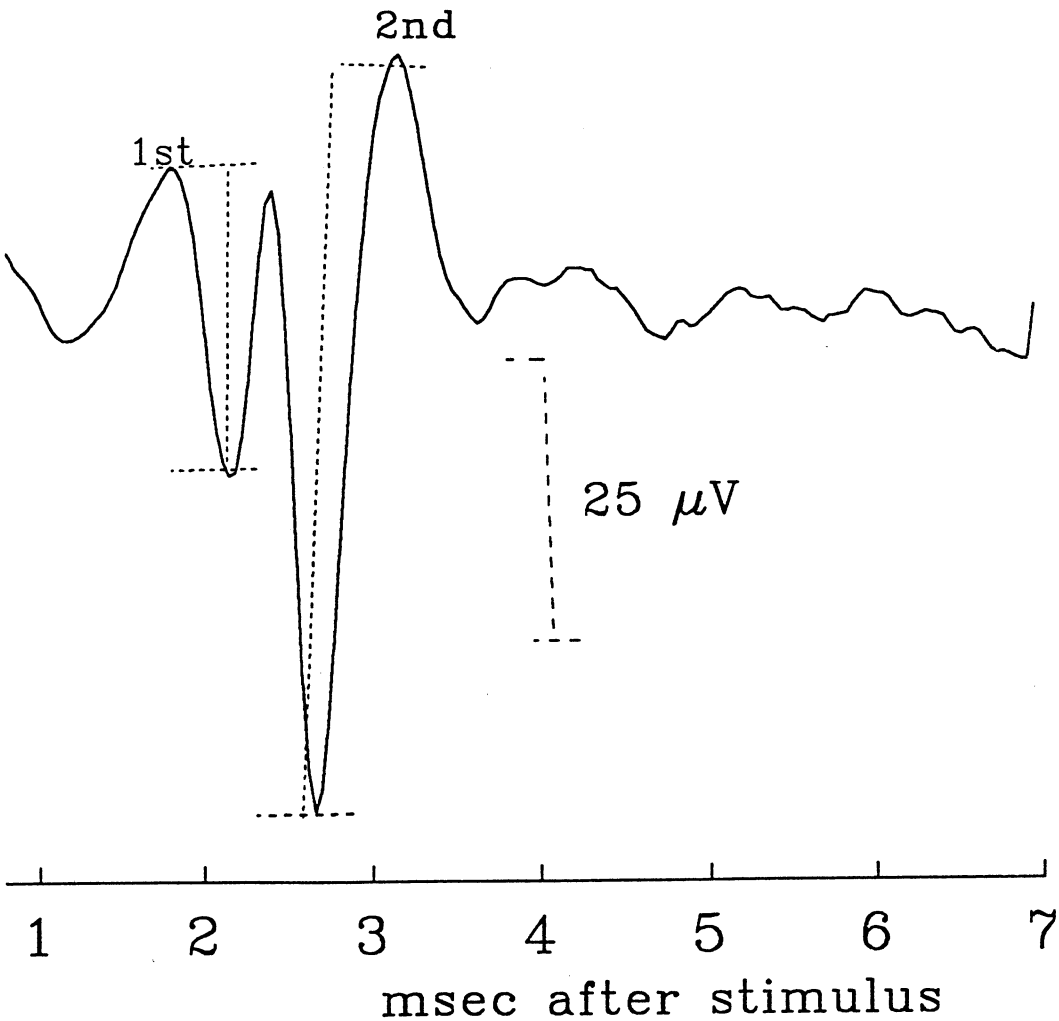

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Figure 2

cn111, 240 days after implantation

Stimulus is artificial voice, 6–32 μA ,250 Hz, 50% duty cycle

Electrode 1,, non-embedded recruitment of early evoked response

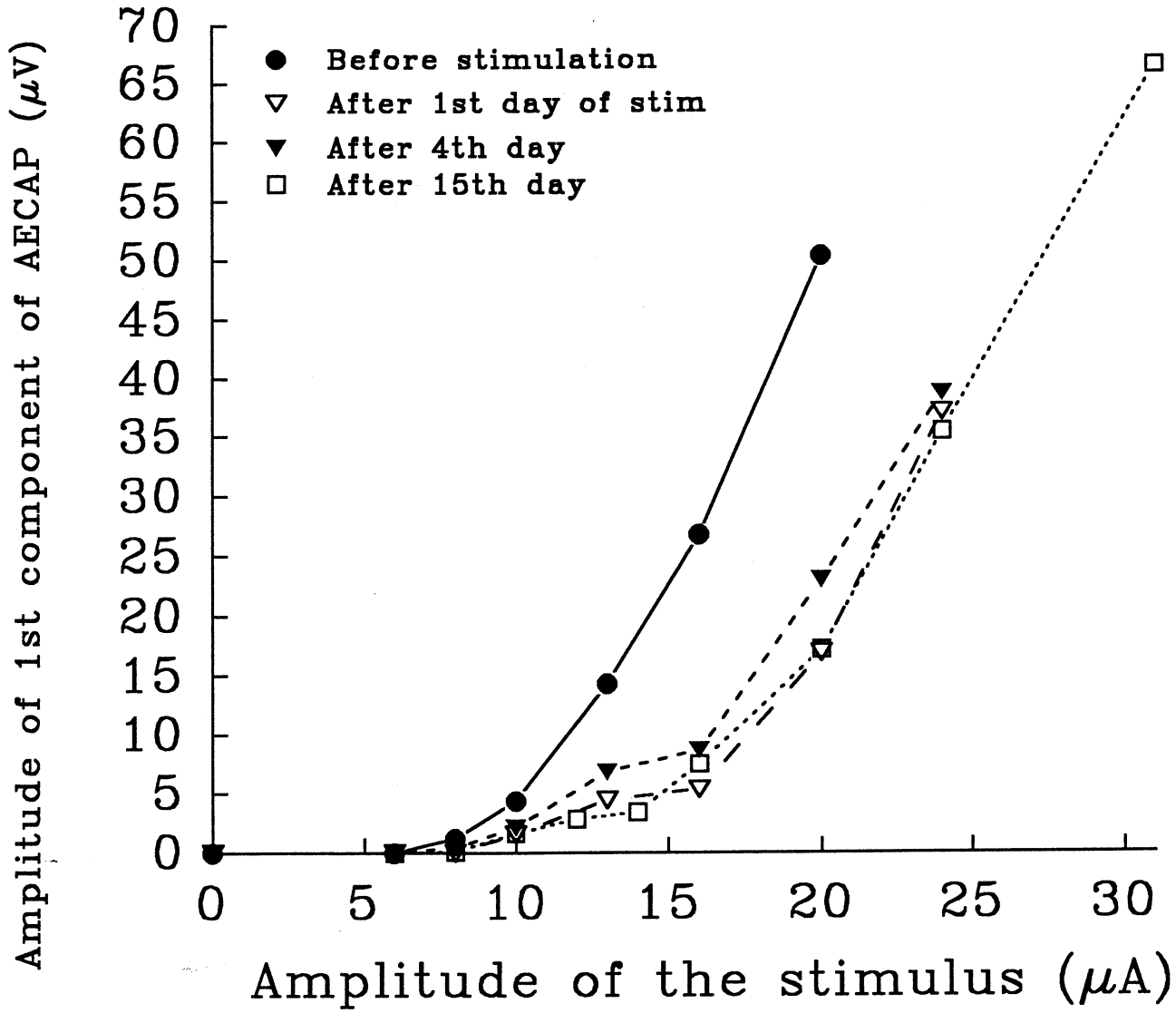

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Figure 3A

cn111, 240 days after implantation

Stimulus is artificial voice, 6–32 μA,250 Hz, 50% duty cycle

Electrode 1,, Embedded recruitment of early evoked response

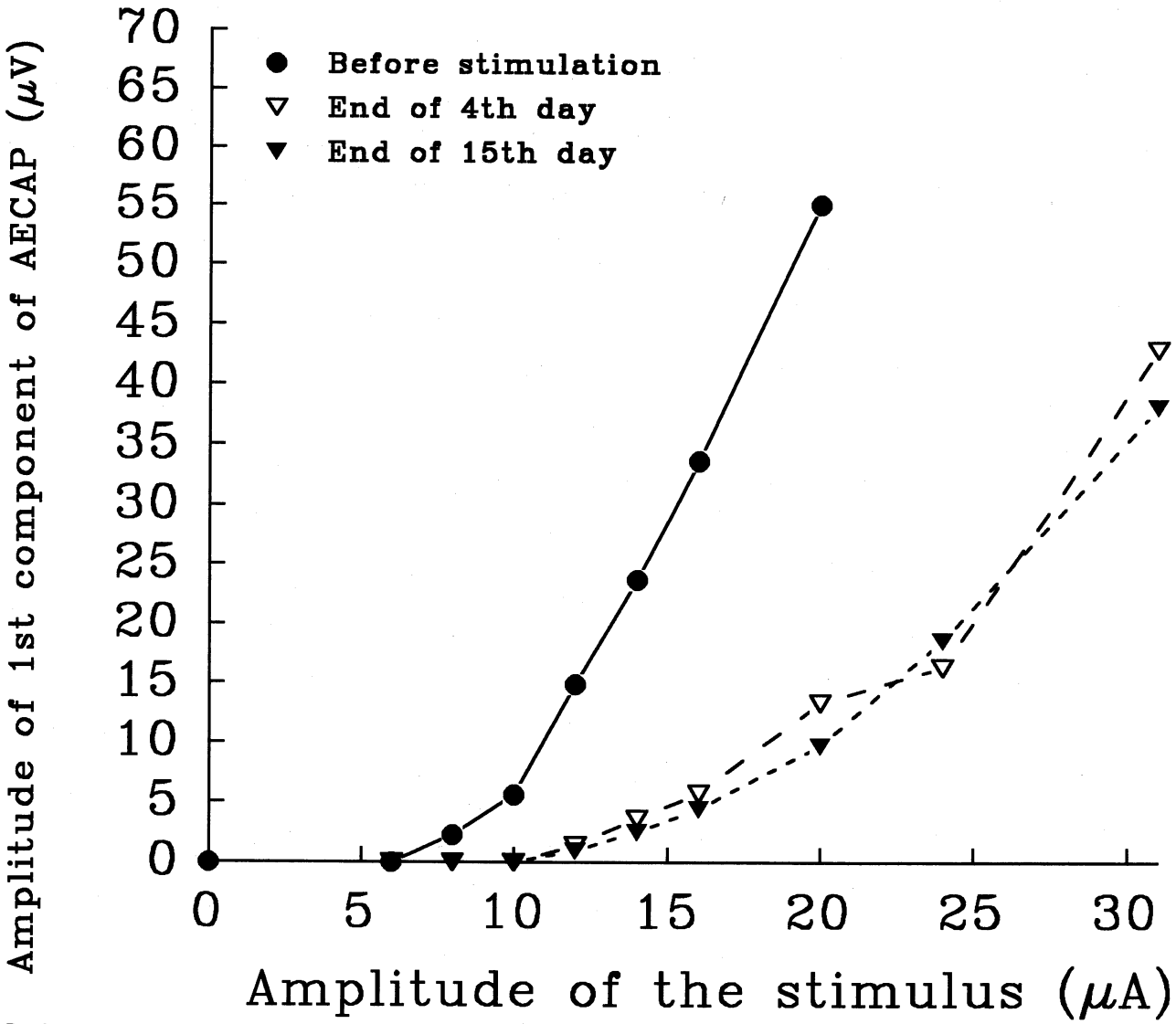

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Figure 3B

cn111, 240 days after implantation

Stimulus is artificial voice, 6–32 μA, 250 Hz, 50% duty cycle

Electrode 3,, non-embedded recruitment of early evoked response

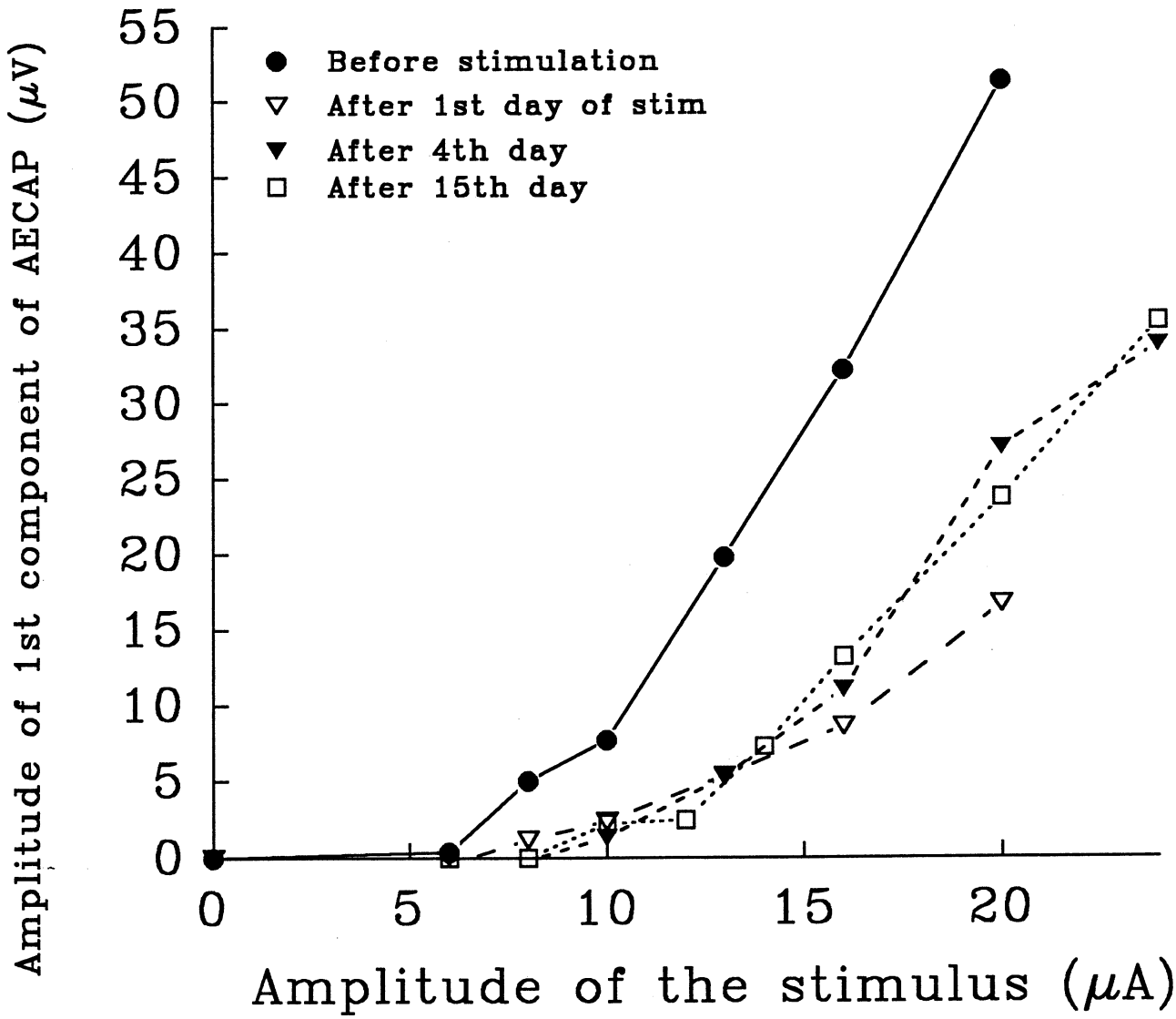

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Figure 3C

cn111, 240 days after implantation

Stimulus is artificial voice, 6–32 μA,250 Hz, 50% duty cycle

Electrode 3,, Embedded recruitment of early evoked response

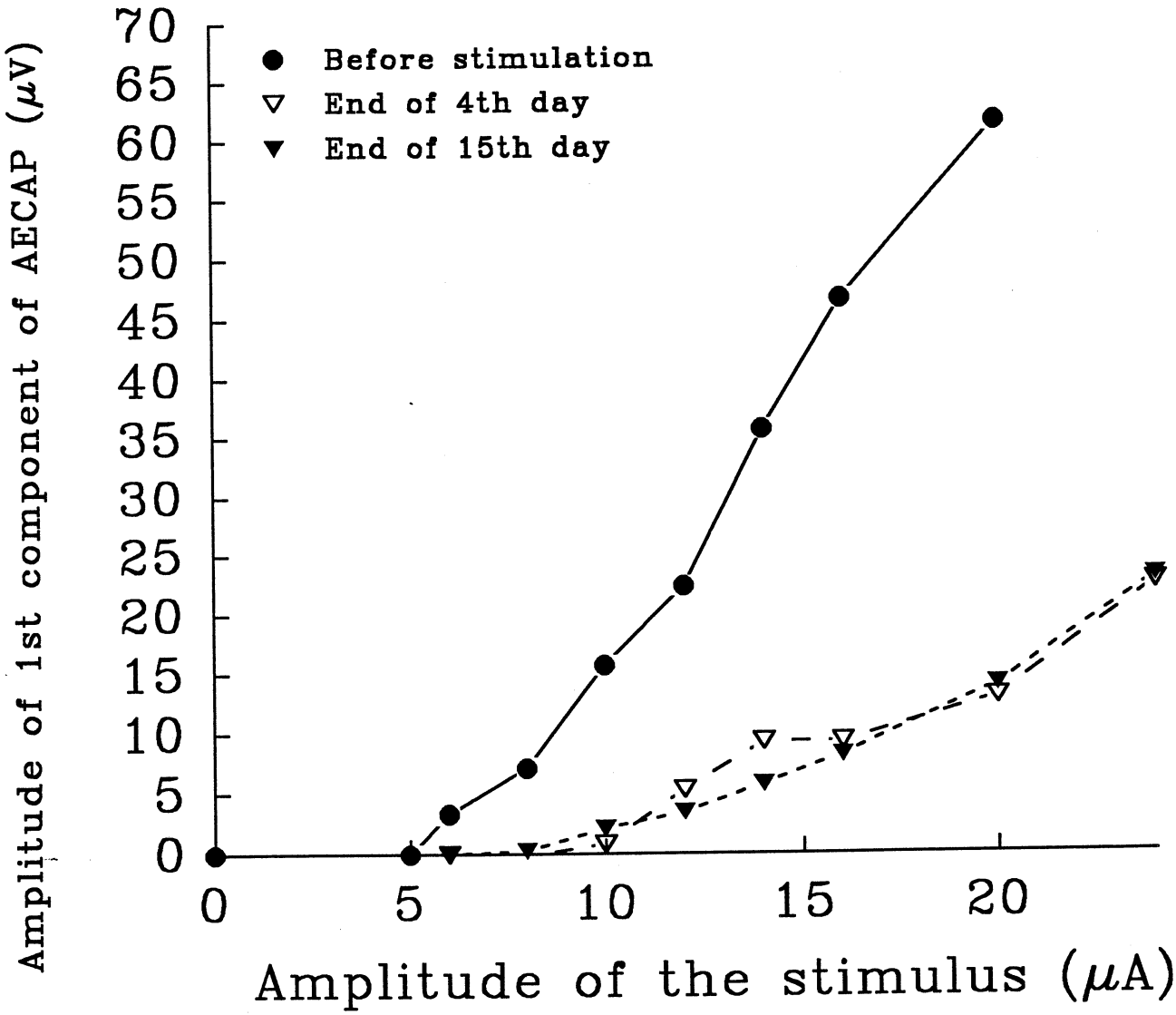

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Figure 3D

cn111, 240 days after implantation

Stimulus is artificial voice, 6–32 μA,250 Hz,50% duty cycle

Electrode 1,, Non–embedded recruitment of second evoked response

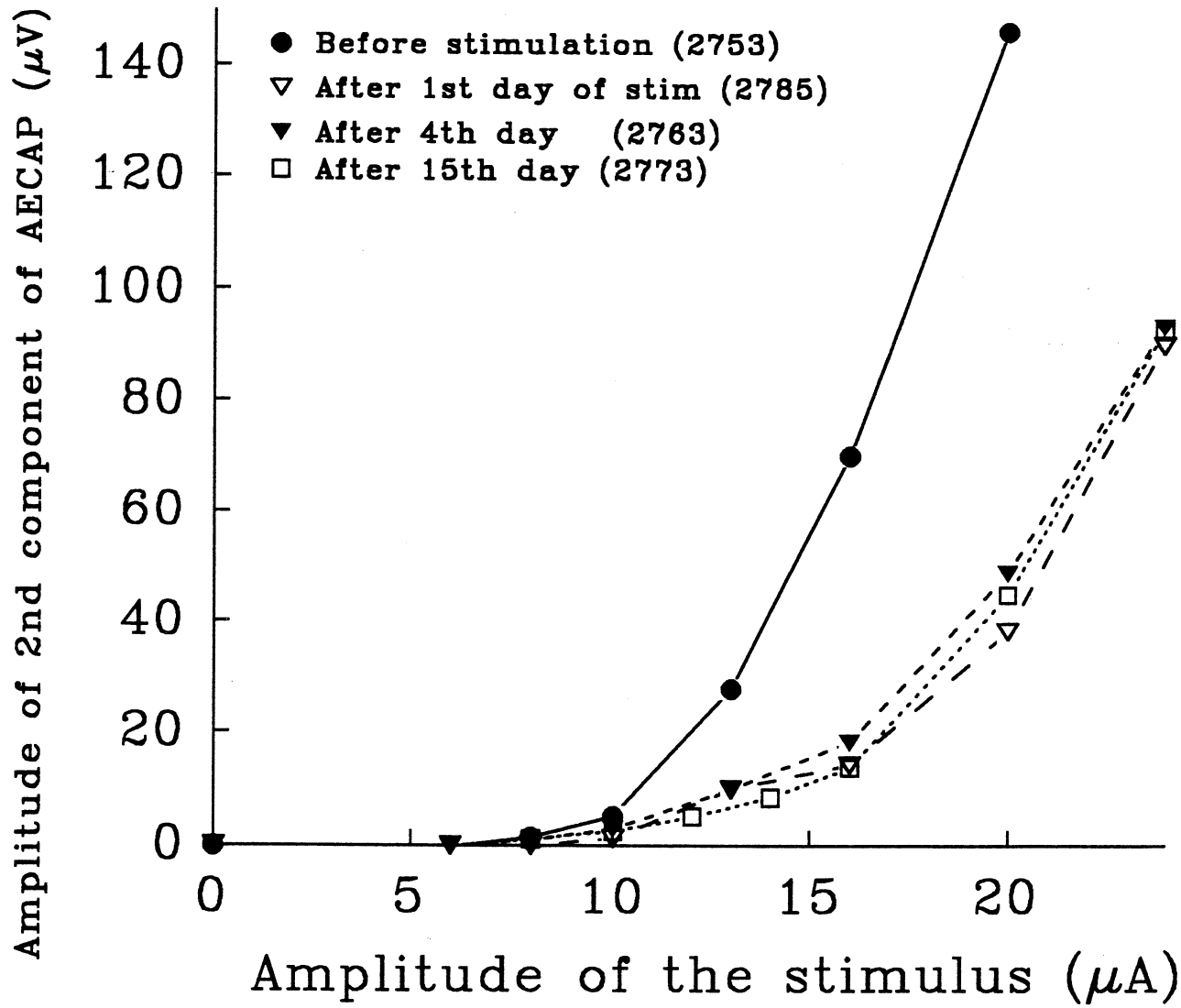

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Figure 3E

cn111, 240 days after implantation

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Electrode 1,, Embedded recruitment of second evoked response

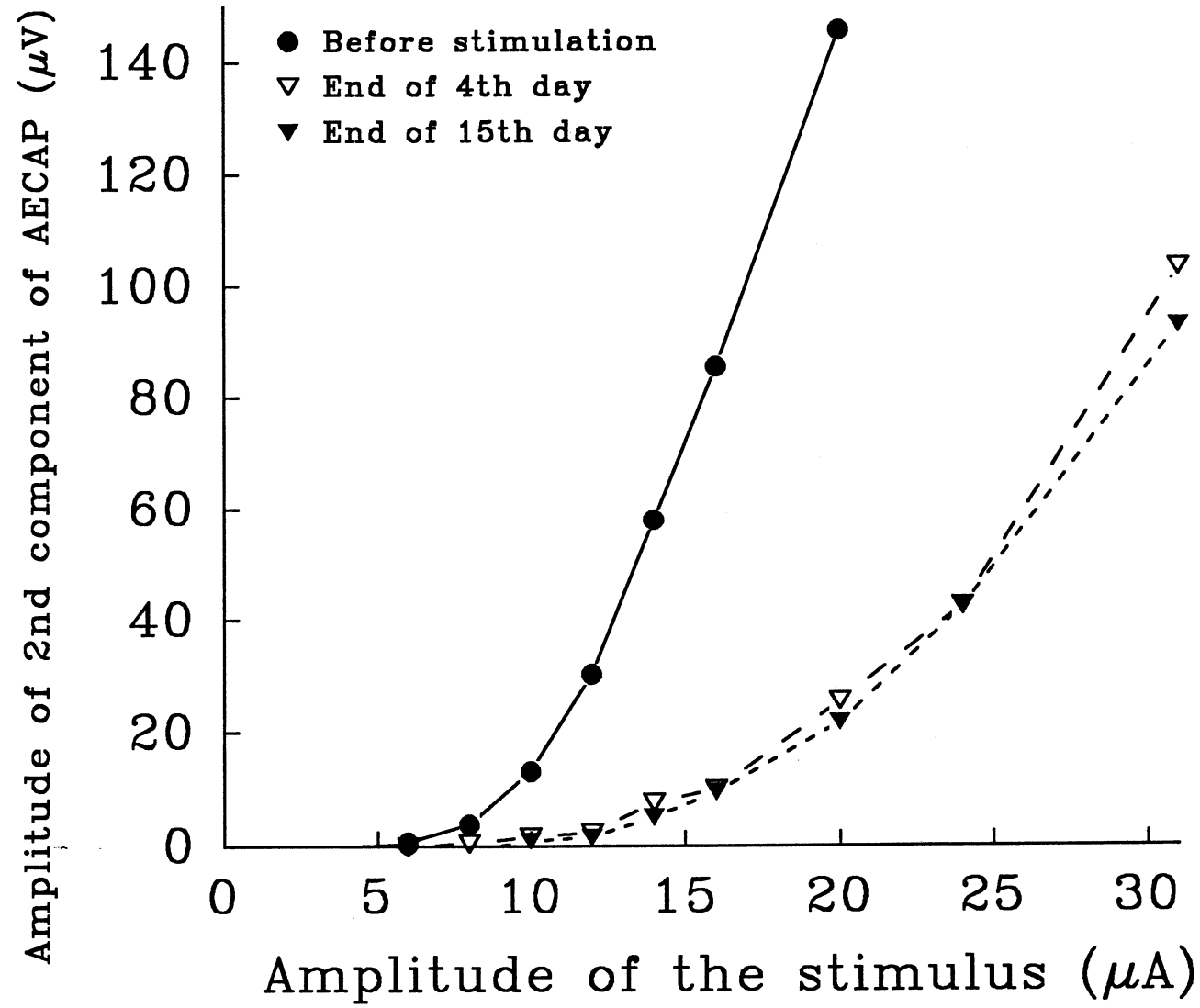

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Figure 3F

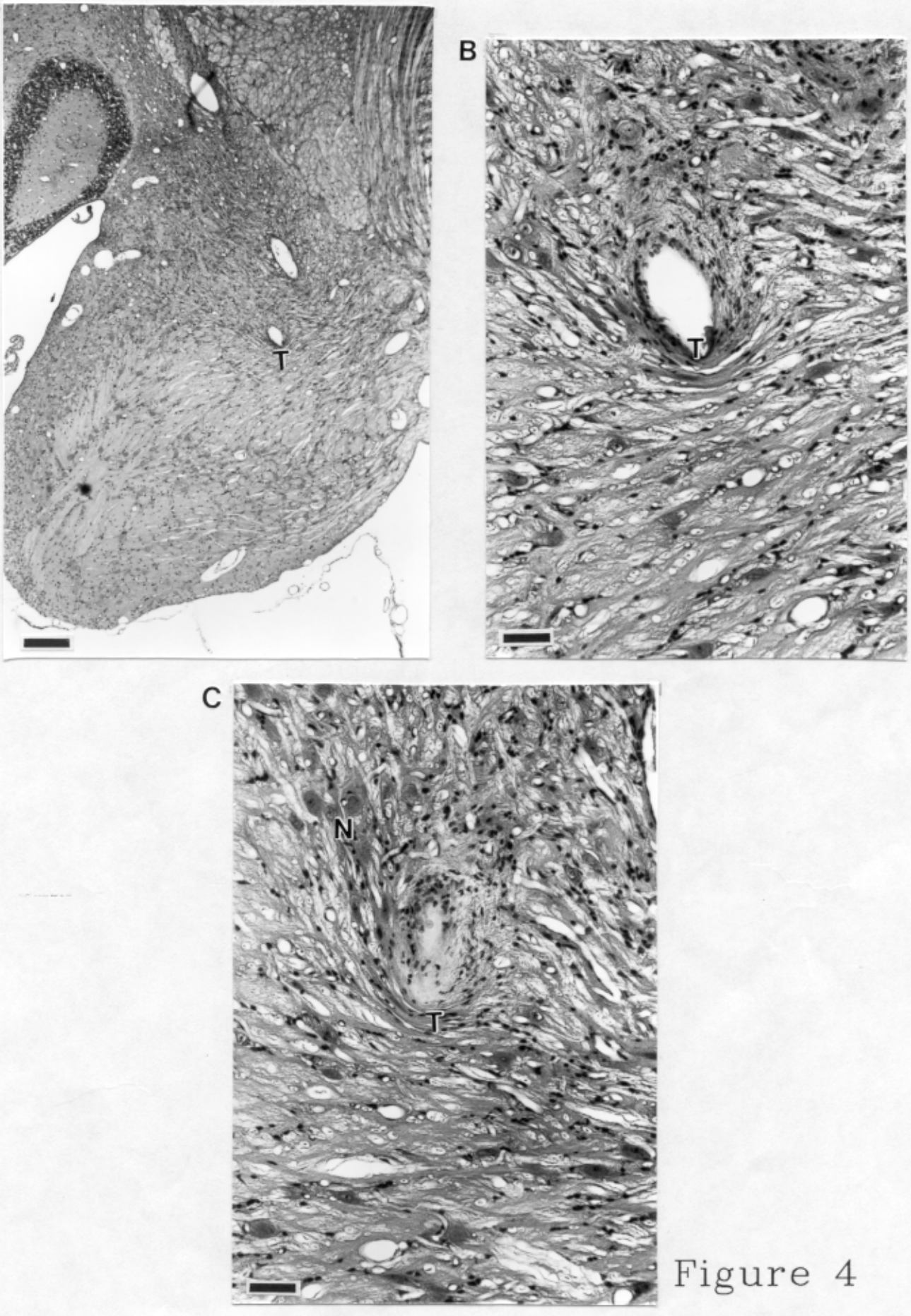
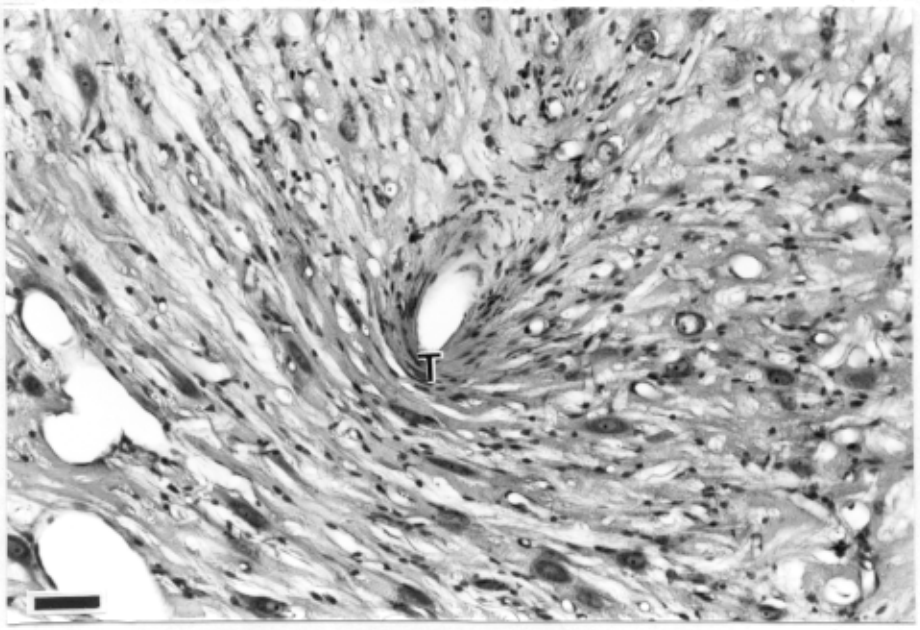


Figure 4

D



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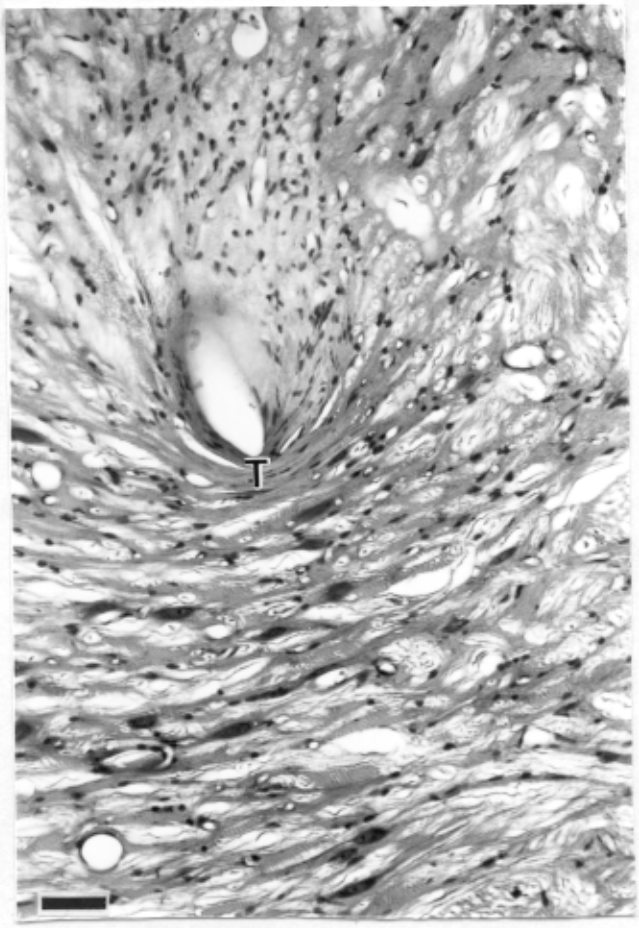

Figure 4

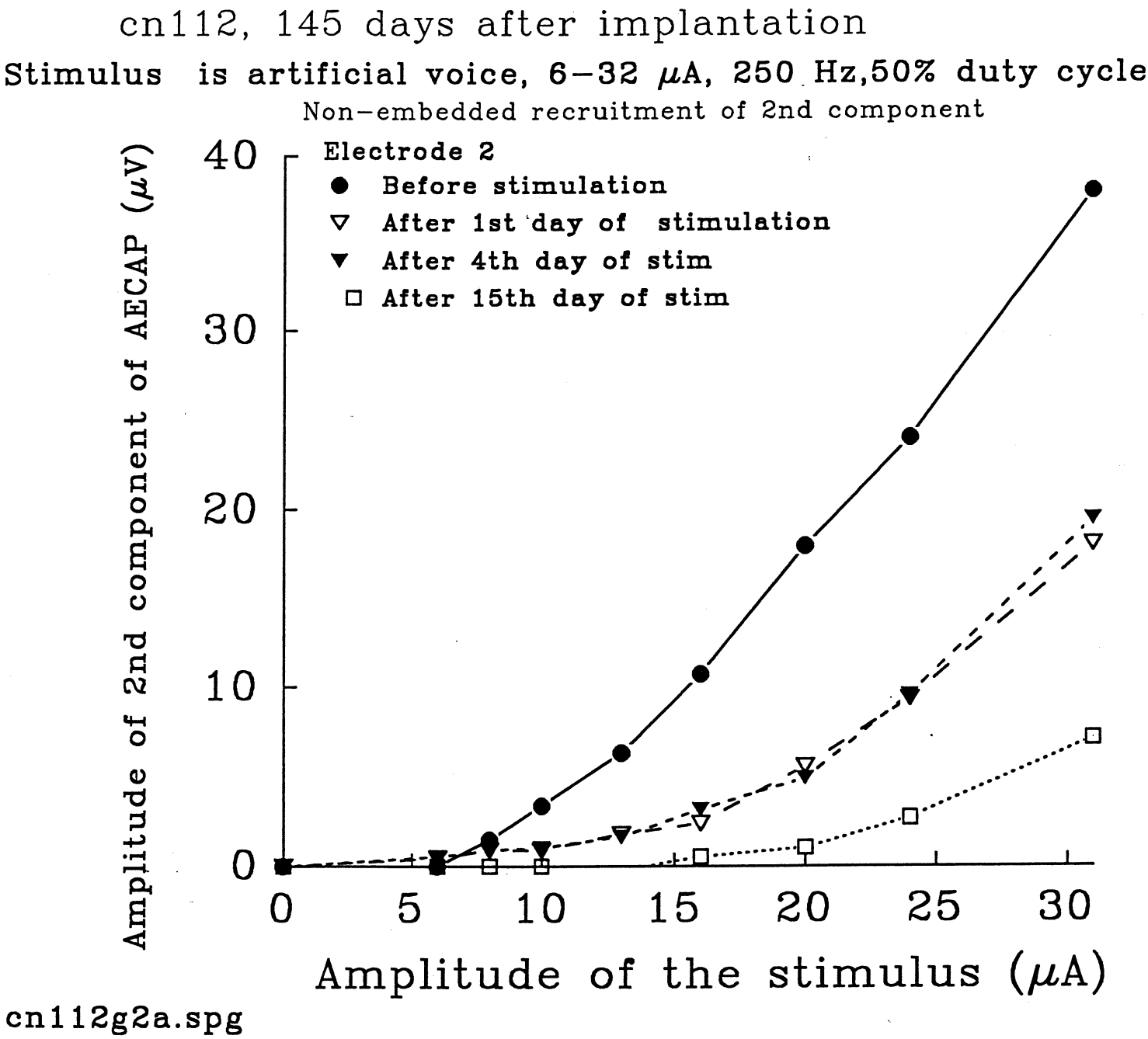
cn112, 145 days after implantation
Stimulus is artificial voice, 6–32 μA, 250 Hz,50% duty cycle
Non-embedded recruitment of 2nd component
Electrode 2
Before stimulation
After 1st day of stimulation
After 4th day of stim
After 15th day of stim
Amplitude of 2nd component of AECAP (μV)
40
30
20
10
0
0
5
10
15
20
25
30
Amplitude of the stimulus (μA)
cn112g2a.spg

Figure 5A

cn112 145 days after implantation

Stimulus is artificial voice, 6–32 μA, 250 Hz, 50% duty cycle

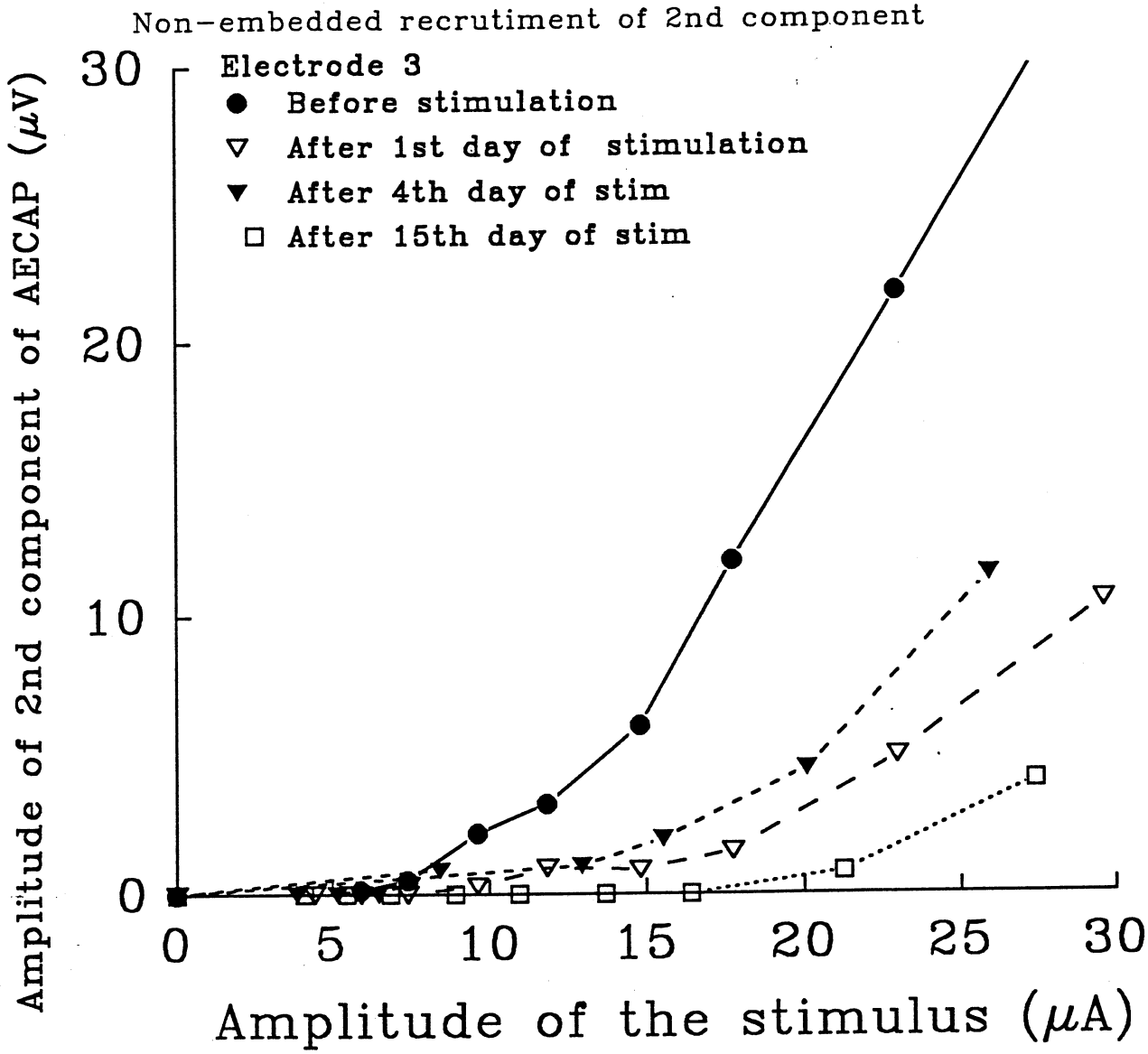

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Figure 5B

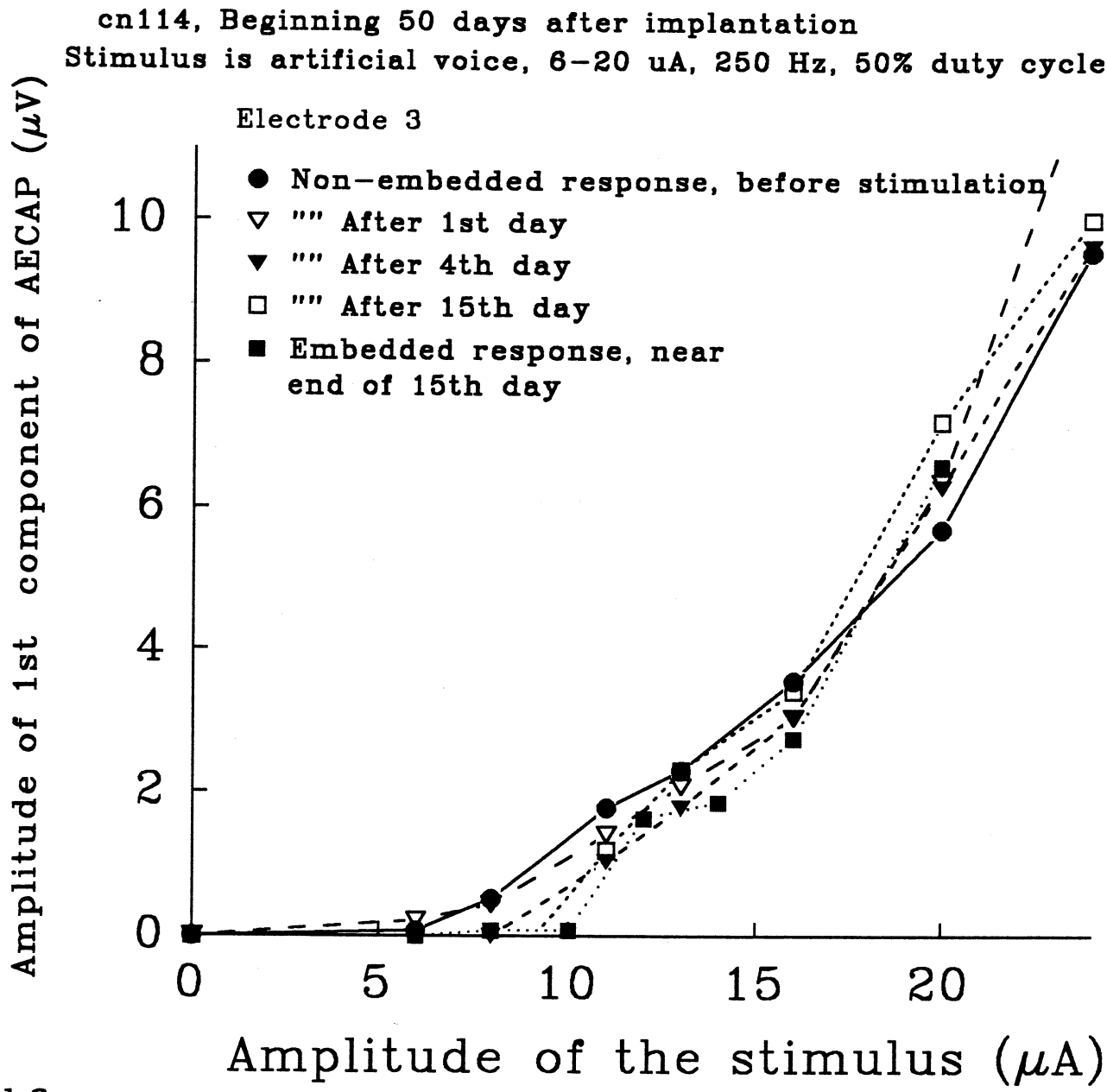

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Figure 6