DISTRIBUTION OF AUDITORY, VISUAL AND SOMATIC SENSORY "ASSOCIATION" RESPONSES IN THE THALAMUS OF CAT

by

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A THESIS

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INTRODUCTION

I

Paul Emil Flechsig, half a century ago, distinguished "association" areas of the cerebral cortex from the primary sensory and motor areas based on anatomic, physiologic and pathologic evidence (16). In so doing, he first verbalized a problem which continues to preoccupy many neurophysiologists and physiological psychologists.

Born in the late nineteenth century empiricist tradition, the "association" areas were soon endowed with a speculative function. They were thought to be those segments of cortex where sensory information was "integrated." The transcortical reflex was proposed as a possible input route (23, 37). Sensory information was thought to be conducted first from the periphery to the primary sensory areas and then, through the cortical substance, to the "association centers." The transcortical reflex construct has permeated (and obscured) thinking regarding these matters until quite recently.

With the availability of more refined recording techniques, came the more precise cerebral localization of peripheral sensory representation. Utilizing oscilloscopic methods to record the evoked potential to peripheral sensory stimulation, certain specific areas of cortex were delimited for each of the stimulus modalities generating activity in the auditory, visual, and somatic sensory systems. Cortical electrical activity known as a "primary response" is a short-latency (7-20 msec.), surface positive (2.5 mv.) potential change. In the cat, if a click is utilized as an auditory stimulus,

primary responses are found on the middle ectosylvian gyrus (51). Similar electrical changes are seen on the posterior lateral gyrus when the stimulus is light flash and on the posterior sigmoid gyrus when electrical shock is applied to the skin of a paw (54).

Definite evoked potentials were not, however, recorded from the "association" cortices until 1953. It was known at that time that chloralose anesthetic agent enhanced cortical relays (2). Amassian, using chloralose, first described definite evoked potentials from the association areas of cortex to auditory and somatic sensory stimulation (6). These responses were noted to be different from primary responses in that, although surface positive, onset latencies are longer (15-30 msec.), amplitude is less (usually less than one mv.), and the duration of positivity is longer.

Buser, Albe-Fessard, Thompson, and colleagues have investigated the cortical association system. In 1955 Albe-Fessard (4) found late responses (60-100 msec.) in cat, to sciatic nerve stimulation, in suprasylvian, anterior lateral, and pericruciate areas of cortex. In a later study (5) she found suprasylvian association responses still present following ablation of the primary somatic sensory areas in cat.

Buser (8) studied the cortical association areas with respect to auditory and visual peripheral stimulation. He found two well defined fields for each modality, located in the same suprasylvian areas in which Albe-Fessard found somesthetic responses. He also corroborated Albe-Fessard's finding regarding the continuing presence of these potentials following ablation of the corresponding primary projection areas. Buser also extensively destroyed the mesencephalic

reticular formation, finding cortical association responses still present.

Thompson and colleagues (50, 51) have since mapped in detail the areas of cortex in cat which respond in the described manner. Four areas are involved, bilaterally. These fields are represented by a focus on the anterior lateral gyrus, another on the cortex surrounding the cruciate sulcus, and two foci on the middle suprasylvian gyrus, one located anteriorly, the other posteriorly. These fields were further found by Thompson to respond in an equal and undifferentiated way to auditory, visual, and somatic sensory stimulation. Responses in these areas are more variable than primary responses in regard to a one to one relationship with the stimulus, but occur similarly and synchronously in all four "association" fields.

The availability of this information placed interested persons in a position to test the transcortical reflex postulate. Thompson and Sindberg (51) demonstrated the unaltered activity of the four association response areas after chronic ablation of AI, AII, Ep, SII, and insular-temporal areas bilaterally. This information implies that input to the association areas is not derived from other cortical areas, as the transcortical reflex theory hypothesizes, but from different sources.

Thompson, Smith and Bliss (52) utilized a technique involving interaction between two afferent volleys to demonstrate common usage of whatever mechanisms are necessary to produce the evoked response. Briefly, this involved, first, demonstrating that two similar stimuli delivered sequentially produced, in the appropriate

primary area, two similar primary responses, provided that the second stimulus was presented at least 0.2 sec. after the first. As the second stimulus was delivered in shorter temporal relationship with the first, the amplitude of the second response progressively decreased until undetectable at an interstimulus interval of approximately 25 msec. This phenomenon was shown to occur with tactile, auditory, and visual stimulation. Applying this technique to the association fields, Thompson et. al. found the same result, with the exception that the refractory periods of the association mechanisms are longer than those of the primary (0.2 sec. absolute refractoriness and 1.0 sec. relative refractoriness). They also found that difference between the two stimuli, using any combination of the three modalities tested, produced the same result. The authors interpreted this as implying that the three modalities utilize a common mechanism, to peripheral stimulation, in the production of the evoked association response.

Single unit recording in the anterior sigmoid gyrus of cats under chloralose was done by Buser and Imbert (10), and in the suprasylvian gyrus in unanesthetized cats by Bental and Bilhari (7). Both groups reported polyvalency of unit response to three modalities (visual, auditory, tactile) in the first instance, and to two modalities (visual, auditory) in the second.

II

The rostral portion of the brain stem ascending reticular activating system is known as the unspecific thalamocortical projection system or the thalamic reticular system. It has been known for some time that these midline thalamic structures (the intralaminar nuclei, including centre median) have been associated with the brain stem

reticular formation (39, 43, 47, 48, 53). Dempsey and Morison, however, first described the anatomic and distinct physiologic characteristics of these structures, in their classic studies of 1941-1942 (11, 12, 13, 14, 38). In cats under nembutal anesthesia, they explored the thalamus with a stimulating electrode while recording from various cortical areas with the electrocorticograph. They were able to distinguish, apart from the well-localized "primary" response, a second category of potential change. This was characterized by the necessity of stimulating at a critical frequency (5-15 per sec.) to produce the response, surface negativity, long latency (20-35 msec.), and a "recruiting" character. By "recruiting," they indicated the increase in amplitude in progressive increments until a maximum level was attained, 2 to 5 responses following initial stimulus application. The cortical distribution of the recruiting response was found to include all parts of exposable cortex, but the greatest activity was found in the gyrus proreus, the anterior sigmoid gyrus, and in the middle and posterior suprasylvian gyri (14). Dempsey and Morison concluded "that there exist between the thalamus and cortex at least two systems, with very different physiological properties: a) the well-known specific projection system with a more or less point to point arrangement; b) a secondary "non-specific" system with diffuse connections" (38).

These authors, shortly after their initial work on the "recruiting" response, described still another category of evoked potential. They found that repetitive stimulation of sensory elements "at any level in the medial lemniscus-internal capsule relay

system" produced a response characterized by short latency, initial surface positivity followed by surface negativity, and localized predominately in the primary areas of cortex. These waves, like the recruiting response, increase progressively in amplitude following stimulation of a specific thalamic nucleus at a frequency of 6-12 per sec. (11, 13). They were called "augmenting responses" by the original authors and were distinguished from the recruiting responses by the characteristics mentioned above.

Those areas of thalamus described as capable of producing recruiting responses by Dempsey and Morison, are areas which undergo retrograde changes of only minor character (40). They were considered to represent an intrathalamic "association" system, interconnecting the various specific relay centers. It was proposed that the recruiting response was transmitted to the cortex via the specific or association nuclei, with synaptic delay (35, 49). Hanbery and Jasper (22), however, proved that this was not the case by selective destruction of the lateral and medial geniculate bodies, VPL, VL, MD, and LP. They were able to produce typical recruiting responses in their lesion animals.

It should be pointed out that the extent of the thalamic recruiting system encompasses more than just the intralaminar nuclei, as originally described. The areas involved include, posteriorly, the supra geniculate area, the rostral pole of centre median, the midline nuclei in the anterior medioventral thalamus, n. ventralis anterior, and the rostral pole of n. reiticularis. Both anatomic and physiologic connections between this system and the specific thalamic nuclei, the hippocampus, the hypothalamus, and the caudate have been demonstrated,

as well as corticopetal projections (21, 43, 46, 47, 48). Starzl and Magoun (46), in 1951, found that these elements formed a "functionally interconnected unit, the excitation of any part of which sets the whole into activity." Enomoto has demonstrated bilateral cortical responses from unilateral activation of the diffuse thalamic system (15). Starzl and Magoun also reported, contrary to Dempsey and Morison's original views, that "responsive cortical zones were found to be relatively specific and delimited, and were distributed in the frontal, cingulate, orbital, parietal, and occipital associational regions."

Repetitive electrical stimulation of these areas at the frequencies mentioned (approximately 6-12 per sec.) produces cortical recruiting waves at about the same frequency as the spontaneous cortical rhythm. It has been shown that, at this frequency of stimulation, the spontaneous rhythms become "in phase" with the recruiting waves. If the stimulus frequency is increased by a factor of two, the spontaneous rhythms disappear. This has implied to some that the unspecific thalamic system may represent a control mechanism in the regulation of the alpha rhythms (24, 25). Microelectrode studies by Li have demonstrated thalamic modulation of cortical unitary responses to specific afferent impulses. He has also found that certain cortical cells may be activated by the thalamic system, which in turn interact with cells usually fired by specific fibres (30, 31).

III

Nineteen-forty-nine was a year in which many of the fundamental aspects of the diffuse thalamic system were described. Also

in 1949, work by Moruzzi and Magoun (39), Lindsley et. al. (32), and French et. al. (19) indicated that the brain stem reticular formation, in the absence of central anesthesia, acted as an ascending and descending neural activating system. Descending influences acted on spinal reflexes or cortically induced movement in either a facilitatory or inhibitory manner, depending upon area of reticular formation stimulated. Cephalic influences of brain stem and diffuse thalamic stimulation were found to be primarily those of EEG desynchronization and behavioral arousal (17, 19, 33). Mesencephalic transection was found to abolish low voltage fast EEG activity and produce a behavioral coma-like state (17, 32).

Reticulocortical transmission pathways were found by Starzl, Taylor, and Magoun (47) to involve the subthalamus, hypothalamus, ventromedial thalamus and internal capsule. This suggested a thalamic path through ventral centre median, ventromedial and ventrolateral nuclei, the lateral wing of the intralaminar nuclei, and ventral ventralis anterior; and an alternative extrathalamic path through the hypothalamus, subthalamus, and internal capsule. After selective destruction of either of these possible routes, lower brain stem stimulation still elicited desynchronization.

The same authors studied input into the reticular substance, and found a large supply of afferent collaterals from the primary auditory and somatic sensory pathways to the midbrain tegmentum, sub and hypothalamus, and ventromedial thalamus (48).

Cephalically, the reticular formation has known connections with the mid-line and intralaminar thalamic nuclei through the lateral

reticulothalmic, tegmental, and tectothalamic tracts (18, 53). Connections are also known to exist between the diffuse thalamic system and the subthalamus (20, 21). Reticulopetal (44) and thalamopetal (45) input from the cerebral cortex has also been demonstrated.

IV

Buser, Albe-Fessard, Thompson, and colleagues have investigated some aspects of certain sub cortical areas demonstrating the "association" response. Albe-Fessard found that responses similar to the late cortical potentials were present in centre median (CM), and that electrical stimulation of CM produced cortical responses similar to those evoked by sciatic stimulation but with shorter latencies (5). Buser's exploration of the thalamus with a recording electrode led him to conclude that the thalamo-cortical pathways mediating visual and auditory association responses are supplied by collateral elements from the primary thalamic nuclei to the thalamic association (not used in the evoked potential sense) nuclei. He further found bimodal (auditory, visual) association-like responses in the lateral posterior thalamic nuclear group; visual responses in the nucleus posterior and dorsal nucleus lateralis posterior; and auditory responses in the inferior nucleus lateralis posterior and the nucleus suprageniculatis. Stimulation of these areas were reported to evoke suprasylvian responses (9).

Contradictory to Buser's conclusions, Thompson and Sindberg (51) found normally responsive association cortex in cats with complete retrograde degeneration of the primary auditory thalamic relay nuclei, following total bilateral ablation of the primary auditory cortical fields.

The present study is an attempt to elucidate some aspects of the organization of diencephalic association response fields and possible corticopetal transmission mechanisms of the evoked potentials which appear on the "association" cortex following peripheral sensory stimulation.

MATERIALS AND METHODS

Procedure

In the present study, an attempt was made to electrically map the distribution of the "association" response to peripheral auditory, visual, and somatic sensory stimulation in the thalamus of cat.

All preparations were acute. A total of 45 cats were studied, all furnished by the University of Oregon Medical School animal supply. The only requirements for selection were that the cats be active, in apparent good health, and weigh at least 2.0 kg.

Cats to be studied were anesthetized with intraperitoneal chloralose (70 mg/kg initially and maintenance doses as needed). One to three hours post injection was required for complete anesthesia.

A tracheostomy was then performed and a tracheal cannula tied into place.

The operation for exposure consisted of removal of both ears and the skin over the top of the head and surrounding the ears. This was accomplished by extending a midline incision (from nasion to occiput) laterally in both directions under both ears until reconnection with the midline occurred posteriorly. These skin flaps were then separated from the animal and the external auditory meatus severed bilaterally, close to the head. All muscle was removed from the right side of the dorsolateral skull surface. The skull was entered by means of a trephine. The bone of the right side of the skull was then removed with rongeurs. The area of brain thus exposed was from the dorsal surface of the frontal lobe anteriorly

to the posterior section of the suprasylvian gyrus. The lateral boundary was the superior section of the ectosylvian gyrus and the medial boundary was the midline. After hemostasis was accomplished with bone wax and Gel Foam, the dura was incised and reflected over this entire area. Care was taken to minimize cortical manipulation. The exposed area was then covered with a saline-soaked gauze "tent," to prevent drying of the cortex. The left upper eyelid and nictitating membrane were then surgically removed, and a drop of atropine sulfate (0.4 mg/cc.) was placed in the conjunctival sac in order to dilate that pupil.

Thus prepared, the cat was placed in a Baltimore stereotaxic headholder fitted with a hollow ear-bar on the left. Headholder and cat were then placed in the stereotaxic instrument, which had previously been calibrated to determine zero-points. A thermostatically controlled heating pad was placed under the cat, in order to maintain normal body temperature. The cat was then curarized, with either d-tubocurarine or decamethonium bromide, and artificially respirated.

Stimulating electrodes were placed in the central and hypothenar ipsilateral anterior paw pads for somatic sensory stimulation. Auditory stimulus was produced by a click from a small speaker placed in a sound proof container, transmitted to the hollow ear-bar by a small piece of plastic tubing. Visual stimulation was provided by a photo-stimulator with a noiseless flash-gun directed at the prepared eye. The application of the stimulus was so arranged that it occurred 10 msec. after the oscilloscope sweep began. Total duration of sweep was 100 msec., and interstimulus interval was 2.0 sec.

Responses were detected by a combination monopolar-bipolar electrode, pre-amplified, and visualized on a dual beam oscilloscope, the upper beam registering the monopolar response and the lower beam registering the bipolar response. Responses were recorded by a camera directed at another dual beam oscilloscope arranged as a "slave" instrument.

The electrode was first placed on the areas of "association" cortex to ensure functionality of the system. The thalamus was then systematically mapped stereotaxically, using Jasper and Ajmone-Marsan's atlas (26) and known responsive areas (geniculate bodies, optic tract, etc.) as guides.

During the exploratory phases of the study, a cortical monitering electrode was placed on the pericruciate association cortex while the thalamus was investigated with a depth electrode. This procedure allowed the experimenter to correlate amplitude and latency of the subcortical vs. the cortical response, to ensure that they were, indeed, similar. The oscilloscopic traces were photographed at 1 mm. dorsoventral and mediolateral intervals in responsive areas. Hand-drawn maps were also made of responsive regions. Iron deposits were made in areas of heaviest response by the application of a current to the electrode tip.

Upon completion of the mapping procedure, the animal was perfused with a solution made up of 3.0 gm. potassium ferrocyanide and 2.7 gm sodium chloride dissolved in 300 cc. of formalin. The perfusion procedure was as follows: 1) The thorax was opened. 2) The descending thoracic aorta was clamped. 3) The pericardial sac

was incised and retracted. 4) The right auricular appendage was incised. 5) The left ventricular wall was perforated. 6) Approximately 300 cc. of the perfusion solution was administered under gravitational pressure through the ventricular perforation. 7) Hand pressure was used to contract the ventricle when necessary. The cat was then replaced in the Baltimore instrument, and a section of brain containing the area mapped was removed. This section was prepared, cut, and tissue slides were made. The sections were stained with cresyl violet, which revealed the site of the ferrocyanide-developed iron deposit. This information was used to verify the anatomic site of the response area. Photographs of the thalamic sections and corresponding oscilloscopic traces will be found in the data section.

Apparatus

The preparatory operation for exposure was accomplished utilizing standard surgical instruments and a Burdick Surgical Unit model SU-4 for dissection and coagulation.

The stereotaxic apparatus used throughout this project was a standard Model U Universal Stereotaxic Apparatus manufactured by Baltimore Instrument Co. with a cat headholder. The only modification of this equipment was replacement of the solid ear-bar on the left with a hollow bar, but similar in all other respects. Stereotaxic zero-points were determined by placing the depth-electrode tip at the junction of the two ear-bars in the mid-line. This point in space represents the zero sagittal and coronal planes as they intersect with the horizontal inter-aural plane. The inter-aural plane is arbitrarily designated as 1 cm. below the zero stereotaxic horizontal

plane. This coordinate system is consistent with the one used by Jasper and Ajmone-Marsan in preparation of their A Stereotaxic Atlas of the Diencephalon of Cat (26), used as a guide in the present study.

Stimuli were produced by Tektronix Type 161 pulse generators, powered by a Tektronix Type 160 A Power Supply. The pulses from the 161's were transmitted to a switching device built by the Research Instrument Shop of the University of Oregon Medical School. This device enabled the experimenter to operate the somatic sensory, auditory, or visual stimulators at will. The switch-box was connected with a Grass Instrument Co. Model PS-2 Photo-Stimulator and noiseless flash-gun for presentation of the visual stimulus. The pulse was amplified by a transistorized amplifier in the switch-box in order to produce a click from a small speaker located in a heavy brass sound-proof container. The click was transmitted to the hollow ear-bar by a short piece of polyethylene tubing for presentation of the auditory stimulus. Somatic sensory stimulation was a shock applied to the ipsilateral forepaw. Shock was delivered through an isolation transformer, driven via the switching mechanism by the 161. The shock electrode was placed in the pads of the ipsilateral forepaw; one pole in the central pad, the other in the hypotenar pad.

Body temperature of the animal was maintained by a heating pad connected to a thermistor unit and rectal probe built by Yellowsprings Instrument Co.

The recording electrode was concentric. It consisted of 0.13 mm. Nichrome wire insulated to the tip and surrounded by a section of 0.43 mm. stainless steel tubing, also insulated, except

at both tips. The inner (wire) pole was connected with two shielded Microdot cables. Each of these cables was fitted into a three-pole plug. Fitted into each of these plugs was an indifferent electrode consisting of a second section of Microdot shielded cable. For monopolar recording, one indifferent was fastened to the skin of the animal. The indifferent used for bipolar recording was fastened to the external, uninsulated, tip of the outer electrode. The cable shielding was grounded to the third pole of each plug. The plugs were connected to separate Tektronix Type 122 Low-Level Pre-Amplifiers (powered by a Tektronix Type PM-125 Power Supply). The pre-amplifiers, in turn, were connected with a Tektronix Type 502 Dual Beam Oscilloscope, each beam recording from a different pre-amplifier. Two Tektronix Type 162 Waveform Generators were used. One of these triggered the oscilloscope every two sec., the other produced a 100 msec. sawtooth corresponding to sweep duration. Pulse output delay by the 161 was set for 10 msec. after the sweep began. The 502 was synchronized with a similar dual beam oscilloscope for photographic purposes. A Grass Model C4C Kymograph Camera was connected through an external electronic shutter (built by the University of Oregon Medical School Instrument Shop) to the "slave" scope. The camera was powered by another Tektronix Type 160A Power Supply and operated with a foot or hand switch by the experimenter. The camera was synchronized with the oscilloscope in such a way that it would expose only once per sweep.

Electrode positions were marked in the thalamus by the electrolytic deposit of iron from electrode tip by connecting the positive pole of a battery to the electrode tip and the negative pole to the indifferent electrode.

A mixture of 95% oxygen and 3% CO_2 was administered through a positive-pressure respirator connected to the tracheal cannula of the curarized animal.

All recording was done in a shielded cage.

Lesions

Two types of lesion animals were used in this study. The first type consisted of otherwise normal cats in which the association cortex had been totally ablated bilaterally. These animals (three were investigated) had been previously used in a conditioning study (28). The ablations had been carried out under aseptic conditions and were of a chronic nature. Anatomically, the lesions included:

1) The entire middle suprasylvian gyrus
2) The anterior one fourth of the lateral gyrus
3) The posterior third of the anterior suprasigmoid and the anterior third of the posterior suprasigmoid, the medial third of the coronal gyrus, and the superficial bank of the cingulate gyrus.

Electrical verification at the time of the experiment, and post-mortem examination indicate that the lesions were indeed complete. Studies in these animals were carried out in precisely the same manner as were studies in normal cats.

The second type of lesion animal studied was one in which the mesencephalic reticular substance had been destroyed electrolytically. In this case, the lesion was made in an acute preparation by coagulation with electrodes powered by the Burdick surgical unit, placed stereotaxically 2 mm. anterior to the inter-aural frontal plane.

The extent of the lesion was determined by post-mortem examination of the brain stem.

RESULTS

Thalamocortical Correlations

Comparisons between responses obtained in "Ep" and "association" thalamus and cortex are presented in Figure 1. The "Ep" cortex, located on the posterior ectosylvian gyrus, is an area responsive to auditory, but not visual or tactile, peripheral stimulation. The evoked potentials are of relatively long latency (15-25 msec.), surface positive and resemble, generally, the association response. The magnocellular region of the medial geniculate body was found to be a subcortical center exhibiting the "Ep" response.[1] Column A of Figure 1 compares the cortical and thalamic association response. The upper trace is cortical; the lower thalamic. Note that response variability is same for both areas in each case. When a thalamic response is present, a cortical response is also present. Note also that the amplitudes vary together. Column B compares association cortex (upper trace) with "Ep" thalamus (magnocellular body). Here there is no correlation between amplitude or variability. In Column C, "Ep" cortex (upper trace) varies in amplitude of response with "Ep" thalamus (lower trace).

Amplitudes of evoked cortical and subcortical (reticular) association responses were measured and a Pearson product-moment correlation coefficient value of 0.94 calculated from 50 consecutive simultaneous recordings from a single subcortical position.

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[1]Personal communication, R. F. Thompson, 1962.

Thalamic Distribution of the Association Response

Photographic maps of the monopolar and bipolar electrical responses to peripheral somatic sensory, auditory and visual stimulation found in five thalamic frontal planes are presented in Figures 2, 4, 6, 8, and 10. Each chart presents data from a single animal, for a total of five cats. Photographic points are, in all cases, in one millimeter steps, as measured by the stereotaxic instrument. The horizontal dispersion represents distance from the midline, located always toward the left; the vertical dispersion represents points superior and inferior to the arbitrary stereotaxic zero-plane. Figures 3, 5, 7, 9, and 11 are photographs of coronal sections of the thalamus of the animals mapped, corresponding to the planes of the response charts. The sections demonstrate the deposits and electrode tracks used for anatomic verification of electrical data.[2]

During the course of this study, characteristic association responses have been seen in several extrathalamic regions of the brain. Widespread areas of the hypothalamus were responsive, as was the dorsal subthalamus, to all three modalities. Trimodal potentials in the hippocampus were often seen when that structure was encountered. In one animal, the amygdaloid complex was encountered. Much of this region responds to auditory and visual, but not to somatic sensory peripheral stimulation.

Figure 2 corresponds to the thalamic frontal plane 2 mm. anterior to the arbitrary inter-aural zero-plane of Jasper and Ajmone-Marsan (26). The upper trace represents the monopolar response; lower trace the bipolar. The respondent region covers an area from

[2]Margins of responsive areas had been previously determined by approaching them from different areas in order to rule out artifact due to tissue damage from the electrode.

approximately 1 mm. above to about 9 mm. below stereotaxic zero, extending from the midline laterally about 5 mm. Thus, the responsive area encompasses the bulk of the mesencephalic reticular substance, central gray, hypothalamus, and the cerebral peduncle. These structures react to ipsilateral forepaw shock, click, and light flash in an undifferentiated manner. The evoked potentials are the intermediate latency, positive deflections characteristic of the "association" response. Note that monopolar traces tend to flatten at a level 6-7 mm. below the stereotaxic zero-point, and then recur further below. At the same position the monopolar responses begin to flatten, the bipolar responses are inverted, but again become positive at a lower depth. The zone of diminished activity most probably represents the junction of the reticular mesencephalon with the cerebral peduncle. The flattening and reversal is not as obvious in the auditory map as in visual and tactile, but the auditory potentials throughout are not as great as corresponding visual and tactile responses. The hippocampus in this animal is not reactive. Anatomic verification for the sight of recording is the tissue section depicted in Figure 3.

Figure 4 represents responses found at approximately the level of Jasper and Ajmone-Marsan's frontal plane 4. Short latency primary potentials are located 4 and 5 mm. above the zero-point at 6 and 7 mm. lateral to the midline on the visual map. This region corresponds with the anatomic location of the lateral geniculate body. Auditory primary responses are noted 6 and 7 mm. lateral to the midline from 1 mm. above to 1 mm. below stereotaxic zero in the anatomic region of the medial geniculate body. Sensory association responses are

found in the midline, and extending 2 mm. lateral therefrom. Dorsoventrally, this field extends from 1 mm. above to 2 mm. below the zero-point. The corresponding anatomic field is the central gray area. Another responsive region extends from ML (mediolateral) plane 4 to plane 7, the bulk of which is located 3 to 4 mm. ventral to stereotaxic zero, but with an upward extension along ML 4 and 5. The ventral block of activity represents the cerebral peduncle. Extending above the peduncle, along planes ML 4 and 5, is evoked activity in the reticular formation and, 2 and 3 mm. above the midline, the suprageniculate area. Figure 5 again demonstrates the stained section corresponding to the plane represented by the response map.

Figure 6, a map of frontal plane 7, is arranged somewhat differently than the other maps. This particular experiment was done prior to construction of the combination electrode. Therefore, alternating columns of bipolar and monopolar responses are depicted. Reactive areas here include zero to minus 4 mm. dorsoventrally in the midline (central gray and hypothalamus), and an area extending from ML 1 to ML 4, 2 mm. above and below the zero-point. The anatomic structure corresponding to this site is the nucleus centre median. A small area on ML plane 5 extending from the zero-line 3 mm. dorsally probably represents the suprageniculate area. The cerebral peduncles were silent in this animal. Primary auditory responses indicate the position of the medial geniculate on ML plane 8. Once again, the amplitudes of the auditory potentials are not as great as those of tactile and visual. Figure 6 includes a drawing from the stained section (Figure 7), outlining the relationships of the prominent nuclei (see legend for definition of abbreviations).

The map of frontal plane 8 (Figures 8 and 9) exhibits two responsive areas, one above and one below the dorsoventral zero-plane. The dorsal field extends from ML plane 1 to ML 4, 1 and 2 mm. above DV (dorsoventral) plane 0. The ventral area involves the region 1 and 2 mm. below DV plane 0, from ML plane 1 to ML 4. Near the midline, the two areas converge. The dorsal area is representative of the anterior pole of centre median, while the ventral field corresponds with the dorsal subthalamus. The isolated response at ML 5, DV minus 3, common to all modalities, probably represents the superior tip of the cerebral peduncle. The reticular nucleus was found not to be responsive at this level.

The visual map of frontal plane 12 (Figure 10) demonstrates the multiple spiked optic tract response 3 to 5 mm below DV zero on ML planes 4 through 6. An association response field is located on ML planes 4 and 5, extending dorsally from the zero-line approximately 3 mm. This area is the anatomic site of ventralis anterior. The rostral reticular nucleus surrounds VA at this level, but it is impossible to distinguish separate fields for the two by this data. Although the rostral pole of the reticular nucleus anterior to this plane has been explored and found to be responsive, it was not systematically mapped in this study. A more ventral association field found 6 and 7 mm. lateral to the midline corresponds to an area of the internal capsule. The midline was completely explored, but no responses could be detected in the area of the nucleus reuniens.

In summary, the following areas of the cat thalamus were found to exhibit an "association" response to peripheral somatic

sensory, auditory, and visual peripheral stimulation which correlated closely with the cortical association response:

1) the suprageniculate nucleus
2) the centre median nucleus
3) the ventral anterior nucleus
4) the rostral pole of the reticular nucleus
5) the central gray area

In addition, the following extrathalamic regions were found to be similarly responsive:

1) the mesencephalic reticular formation
2) the hypothalamus
3) the cerebral peduncle
4) the hippocampus
5) the dorsal subthalamus
6) anterior limb of the internal capsule

The photographic maps demonstrate that these areas respond in a discrete fashion, with the characteristic wave-like, long-latency "association" response. The visual potentials, cortical and subcortical, always exhibit a longer onset latency than do auditory and tactile. Thalamic association responses are similar to those seen on the cortex and are readily distinguished from surrounding areas. It will be noted that the bipolar response is, in general, more specific than is the monopolar response, beginning later and ending earlier. This is probably due to the monopolar electrode's propensity for recording potential change through volume conduction.

Subcortical intermodality interactions were studied in the manner described in the introductory section of this paper. Both

reticular and thalamic (centre median) recovery cycles for association responses to the same stimulus repeated twice and for all pairings of the three stimulus modalities were indistinguishable.

Lesion Studies

Three cats with total bilateral chronic ablations of the association cortex, and one cat with total electrolytic destruction of the mesencephalic reticular substance at the level of frontal plane 2 were studied. The lesion animals were done as preliminaries for a more complete later investigation.

Ablated Animals

Although the described reticular and thalamic fields were found to be responsive in the cats with bilateral association cortex ablations, less of their area seemed to be involved. Response fields of 1 to 2 mm. size were found scattered through the reticular formation, centre median, and ventralis anterior. The response to auditory stimulation was found, at very low amplitude and in the reticular formation solely, in only one of the three cats. Visual responses were found in both thalamus and reticular formation, but, again, at low amplitudes. The tactile response, except for the lesser area of distribution, appeared as in the intact animal.

Reticular Lesion

Electrolytic destruction of the mesencephalic reticular substance at the level of frontal plane 2 effectively abolished pericruciate cortical and thalamic (centre median and ventralis anterior) association responses to ipsilateral forepaw shock and

click. Visual responses of much decreased amplitude could be elicited in the thalamus. The cortical visual response was still present, but at a moderately diminished amplitude.

FIGURE 1

Demonstration of thalamocortical response correlation technique used for identification of thalamic "association" responses.

Column A is a series of simultaneous responses in association cortex (upper trace) and "association" thalamus (lower trace). Note correlation of response amplitude.

Column B is a similar series, but comparing association cortex (upper trace) with "Ep" thalamus (magnacellular body). In this instance, a lack of amplitude correlation is noted.

Column C compares Ep cortex (posterior ectosylvian) with "Ep" thalamus. Thalamic response amplitude varies with cortical amplitude.

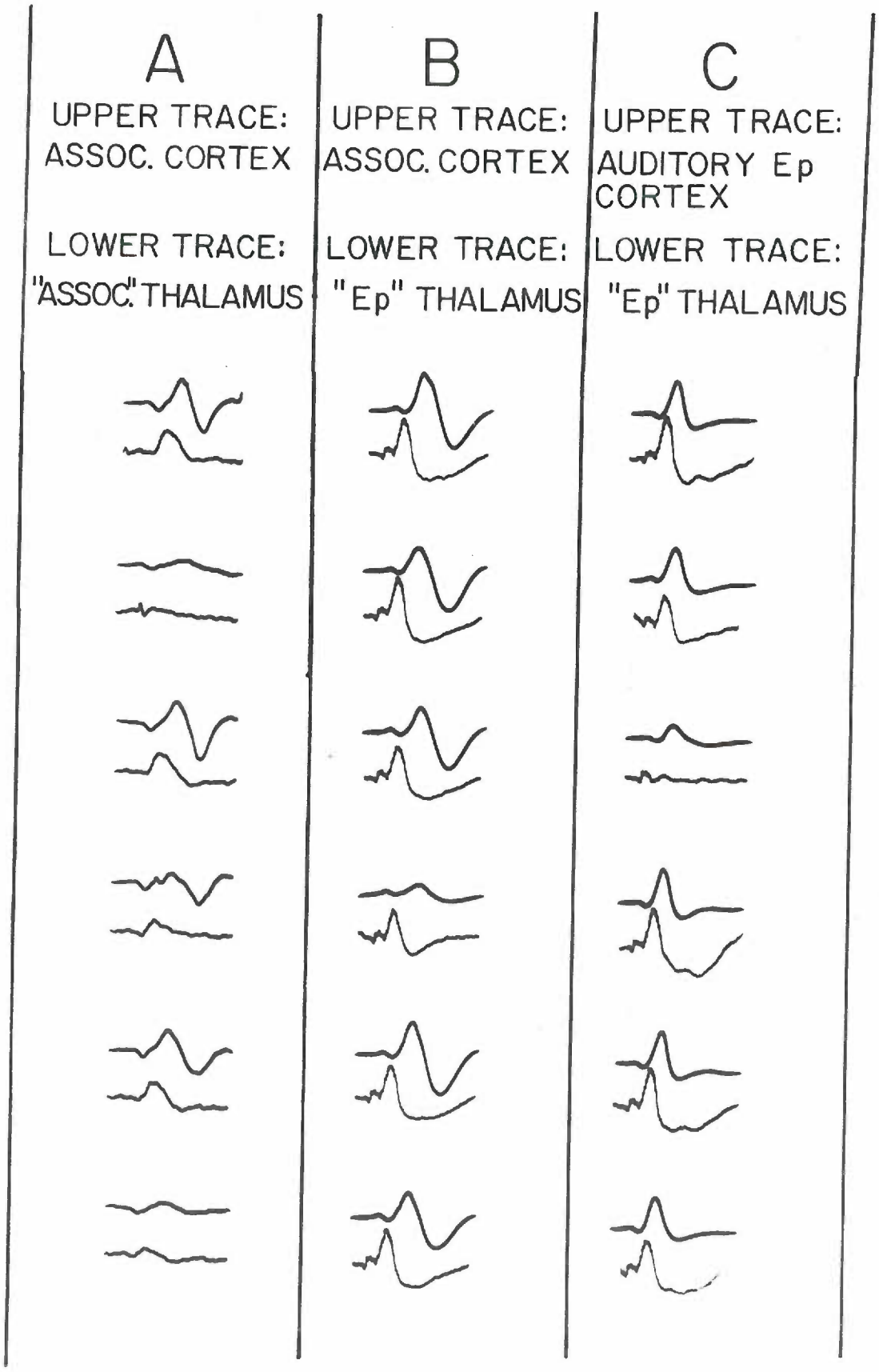
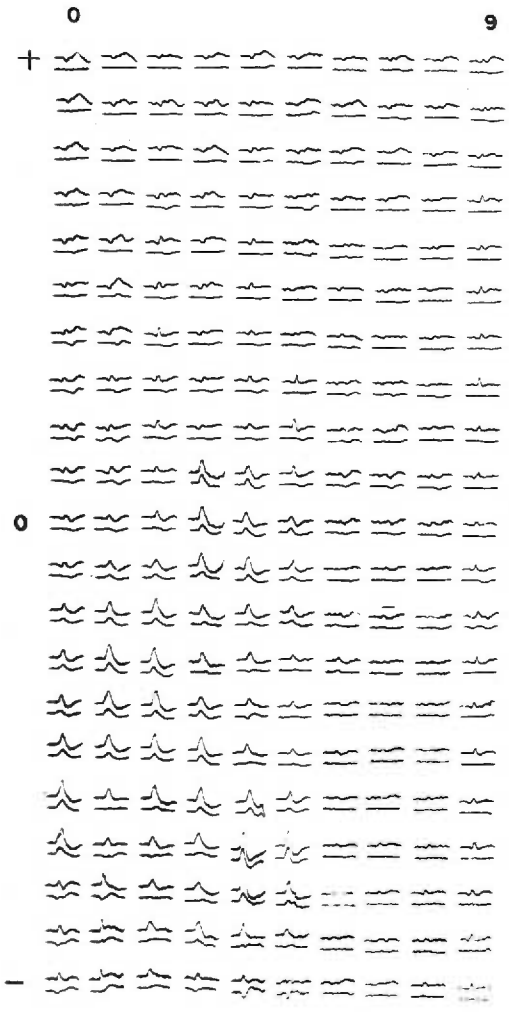

A
UPPER TRACE:
ASSOC. CORTEX
LOWER TRACE:
"ASSOC." THALAMUS
B
UPPER TRACE:
ASSOC. CORTEX
LOWER TRACE:
"Ep" THALAMUS
C
UPPER TRACE:
AUDITORY Ep
CORTEX
LOWER TRACE:
"Ep" THALAMUS

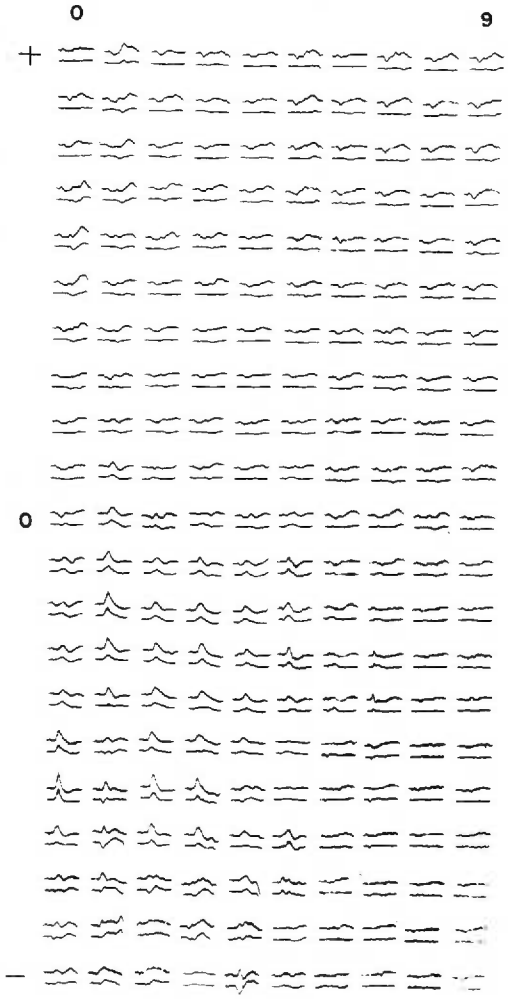
FIGURE 2

Tactile, auditory, and visual response map of thalamic frontal plane 2. Upper trace is monopolar, lower trace is bipolar response. Horizontal and vertical separation of traces is in one millimeter steps. Horizontal zero (0) represents the thalamic midline. Vertical zero is stereotaxic dorsoventral zero plane, located 10 mm. above the horizontal inter-aural plane.

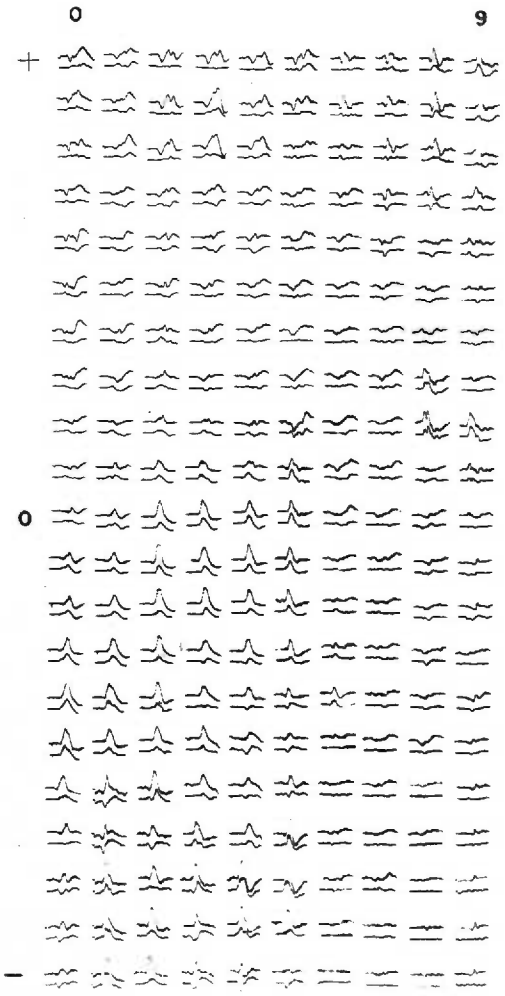
Note that an area responsive to all three modalities extends from the midline laterally 4-5 mm., and ventrally from the dorsoventral zero plane 8-9 mm. This area includes the mesencephalic reticular formation, central gray, hypothalamus, and cerebral peduncles (see Figure 3, anatomic section).



SHOCK TO IPSILATERAL FOREPAW



CLICK



LIGHT FLASH

UPPER TRACE MONOPOLAR

LOWER TRACE BIPOLAR

FRONTAL 20

FIGURE 3

Anatomic tissue section, demonstrating electrode tracks, corresponds to plane mapped in Figure 2. Section is taken at the level of thalamic frontal plane 2.

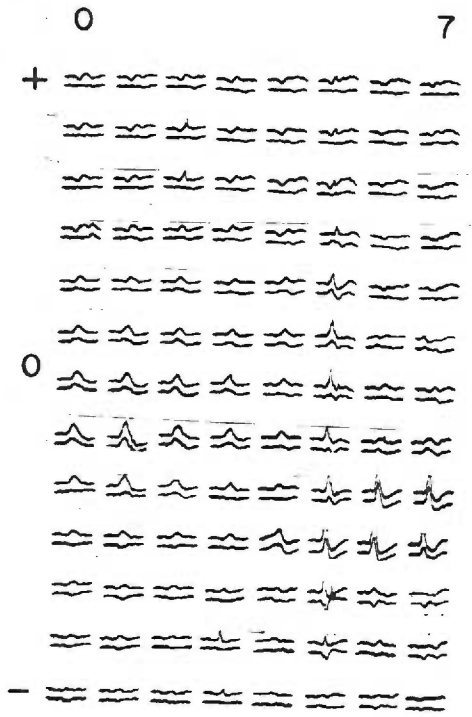
Note central gray, superior colliculus, cerebral peduncle, geniculate bodies as landmarks.

FIGURE 4

Map of responsive areas of frontal plane 4.

Note short latency visual primary responses in lateral geniculate body 4 and 5 mm. above the zero plane at 6 and 7 mm. lateral to the midline on the visual map. Auditory primaries in the medial geniculate body are found, on the auditory map, 6 and 7 mm. lateral to the midline from 1 mm. above and 1 mm. below stereotaxic zero.

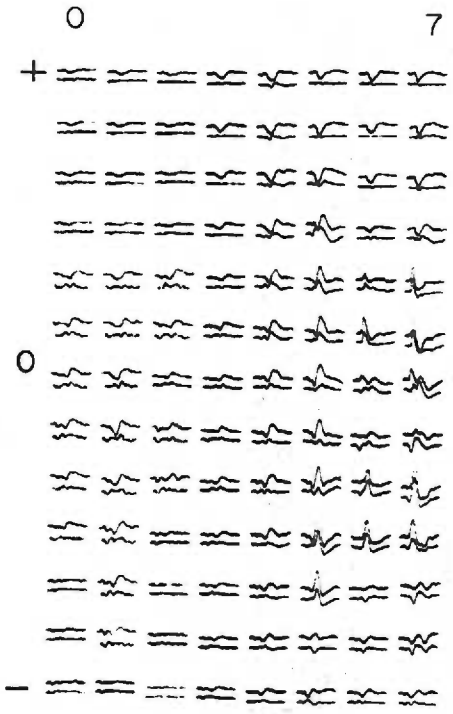
Sensory association responses are seen in the midline, extending 2 mm. laterally and from 1 mm. above to 2 mm. below the zero-plane. This area corresponds with the central gray area. A more lateral area is located from ML 4 to ML 7, 3 to 4 mm. below zero. This is the area of the cerebral peduncle. An upward extension of activity along ML4 and ML 5 represents responsiveness in the reticular formation and supragenicular area.



SHOCK TO IPSILATERAL FOREPAW

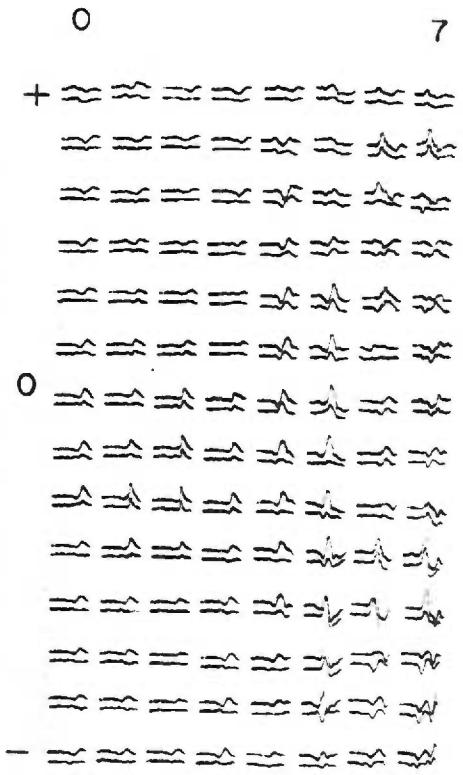
1mV

50msec



CLICK

FRONTAL 4.0



LIGHT FLASH

UPPER TRACE MONOPOLAR

LOWER TRACE BIPOLAR

FIGURE 5

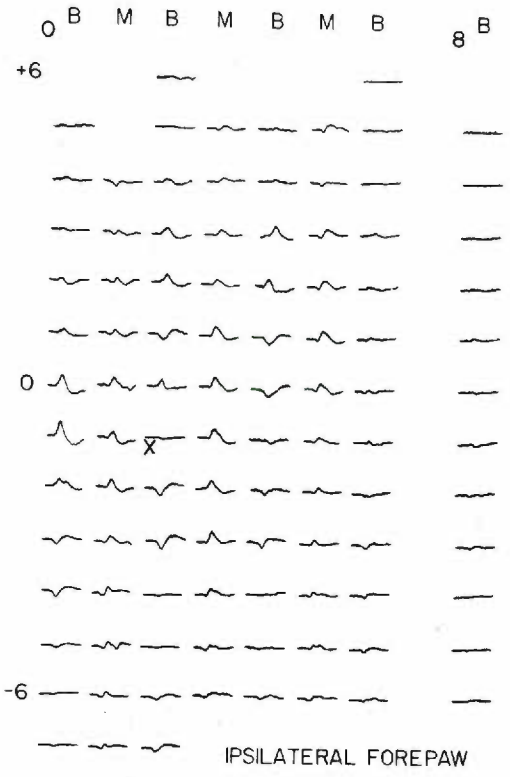
Thalamic tissue section corresponding to map in Figure 4. The section is at frontal plane 4. The medial and lateral geniculate bodies, optic tract, and cerebral peduncles serve as landmarks.

FIGURE 6

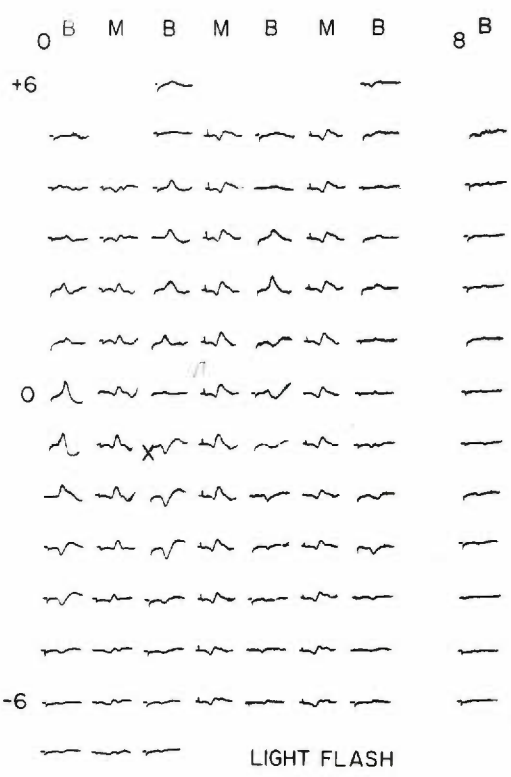
Response map of frontal plane 7. B and M refer to alternating rows of bipolar and monopolar recording. Otherwise, the maps are read the same as those preceding.

The responsive areas include zero to minus 4 dorsoventrally in the midline (central gray and hypothalamus), and an area extending from ML 1 to ML 4, 2 mm. above and below the zero point. The corresponding anatomic structure is centre median.

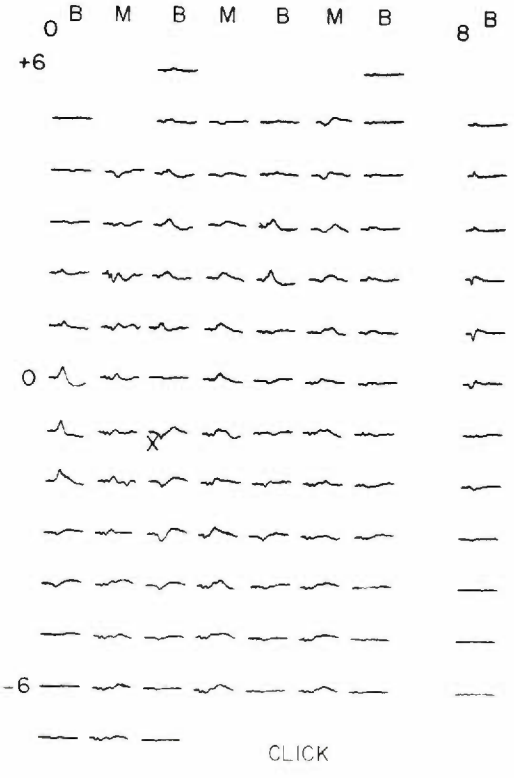
This figure includes a drawing of the tissue section seen in Figure 7. Hbl = lateral habenular nucleus; MD = medial dorsal nucleus; CM = centre median; LP = lateral posterior nuclear area; SG = suprageniculate area; GM = medial geniculate; NR = red nucleus; THP = habenulopeduncular tract; x = deposit site.



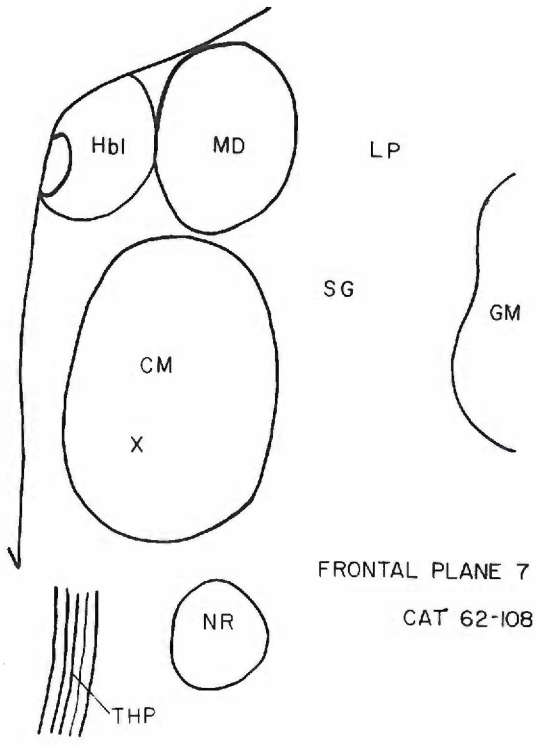
IPSILATERAL FOREPAW



LIGHT FLASH



CLICK



FRONTAL PLANE 7

CAT 62-108

FIGURE 7

Thalamic tissue section corresponding to response map in Figure 6. Section is taken at the level of frontal plane 7. The habenular nuclei, medial and lateral geniculate bodies, cerebral peduncle and habenulopeduncular tract serve as landmarks. Note deposit site in centre median.

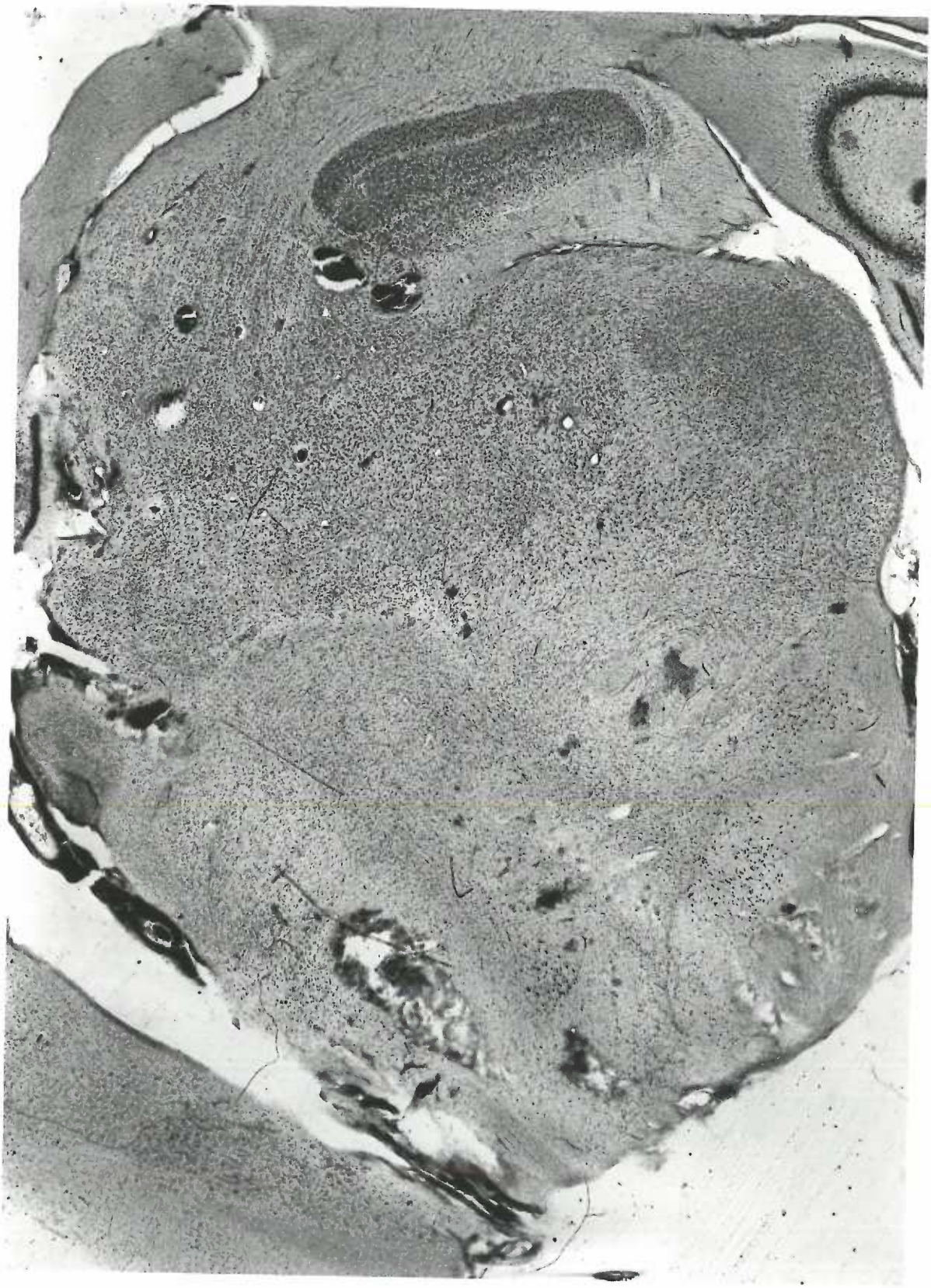


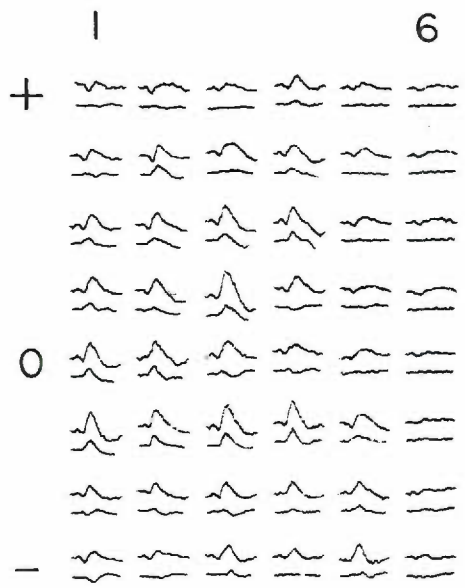
FIGURE 8

Map of association response fields located on frontal plane 8.

Two responsive areas are noted, one above and one below stereotaxic zero. The dorsal field extends from ML 1 to ML 4, and 2 mm. above dorsoventral zero. The ventral area extends from ML 1 to ML 4, and 2 mm. below DV zero.

The dorsal field is the rostral pole of centre median, the ventral area is the dorsal subthalamus.

An isolated response, common to all modalities, at ML 5, minus 3, probably represents the superior tip of the cerebral peduncle.

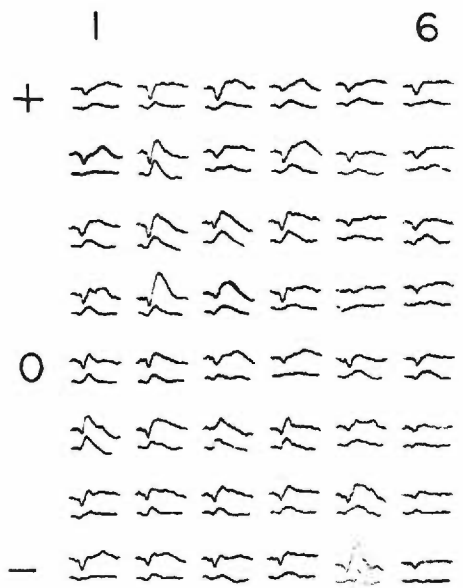


SHOCK TO IPSILATERAL

FOREPAW

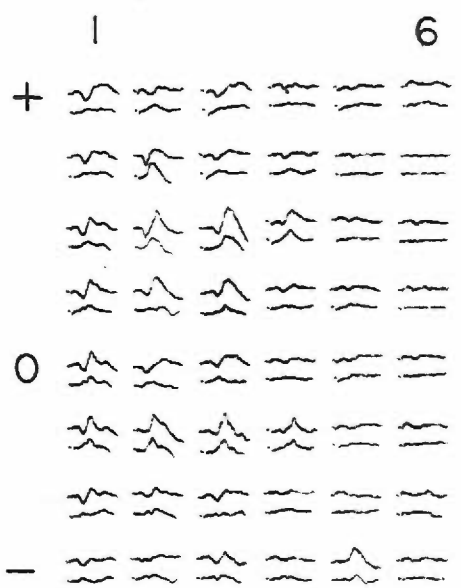
1mV

50msec



CLICK

FRONTAL 8.0



LIGHT FLASH

UPPER TRACE MONOPOLAR

LOWER TRACE BIPOLAR

FIGURE 9

Thalamic tissue section corresponding to response map in Figure 8. Section is at the level of frontal plane 8. Habenular nuclei, lateral geniculate body, optic tract, subthalamus, and centre median serve as landmarks.

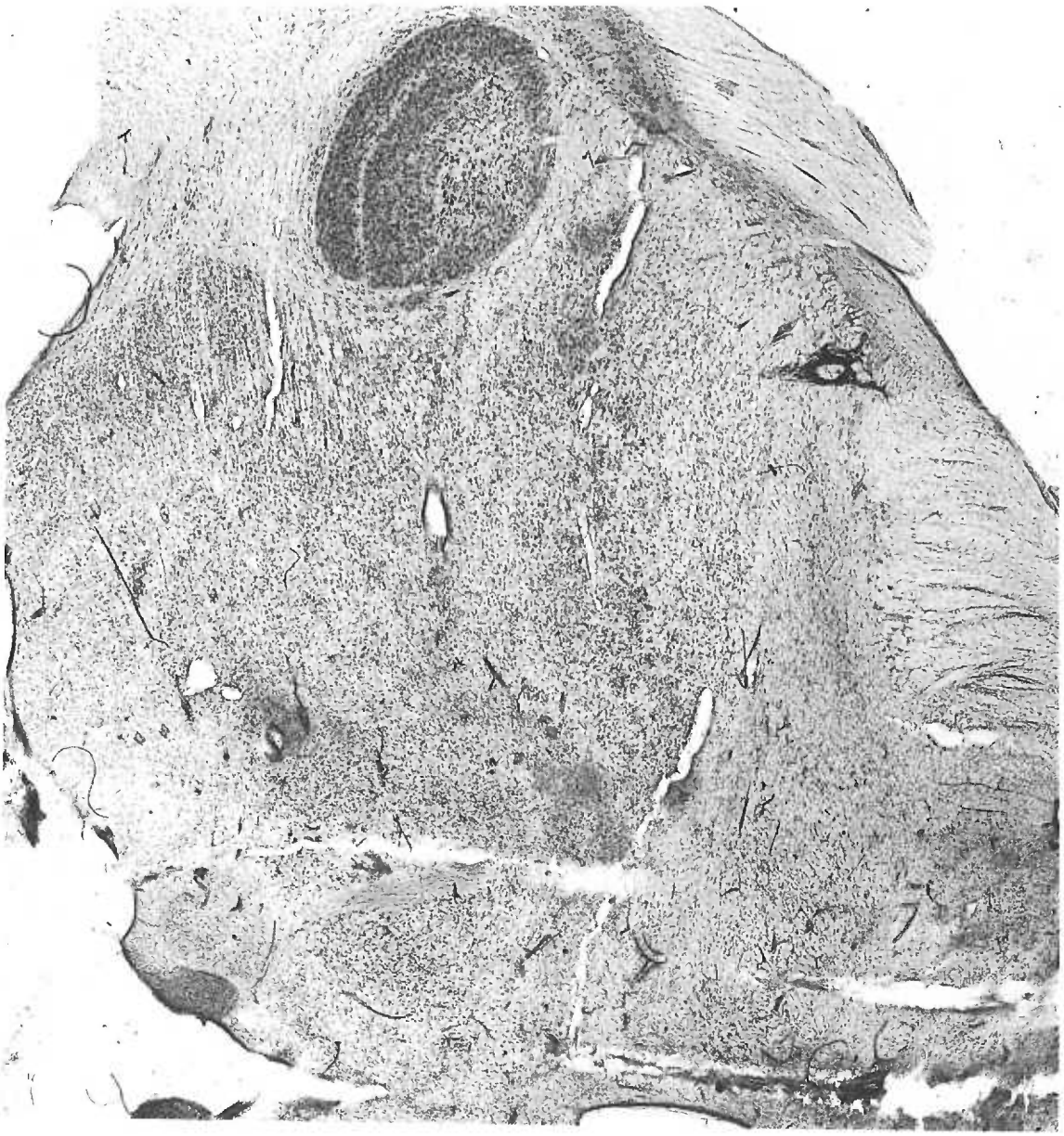
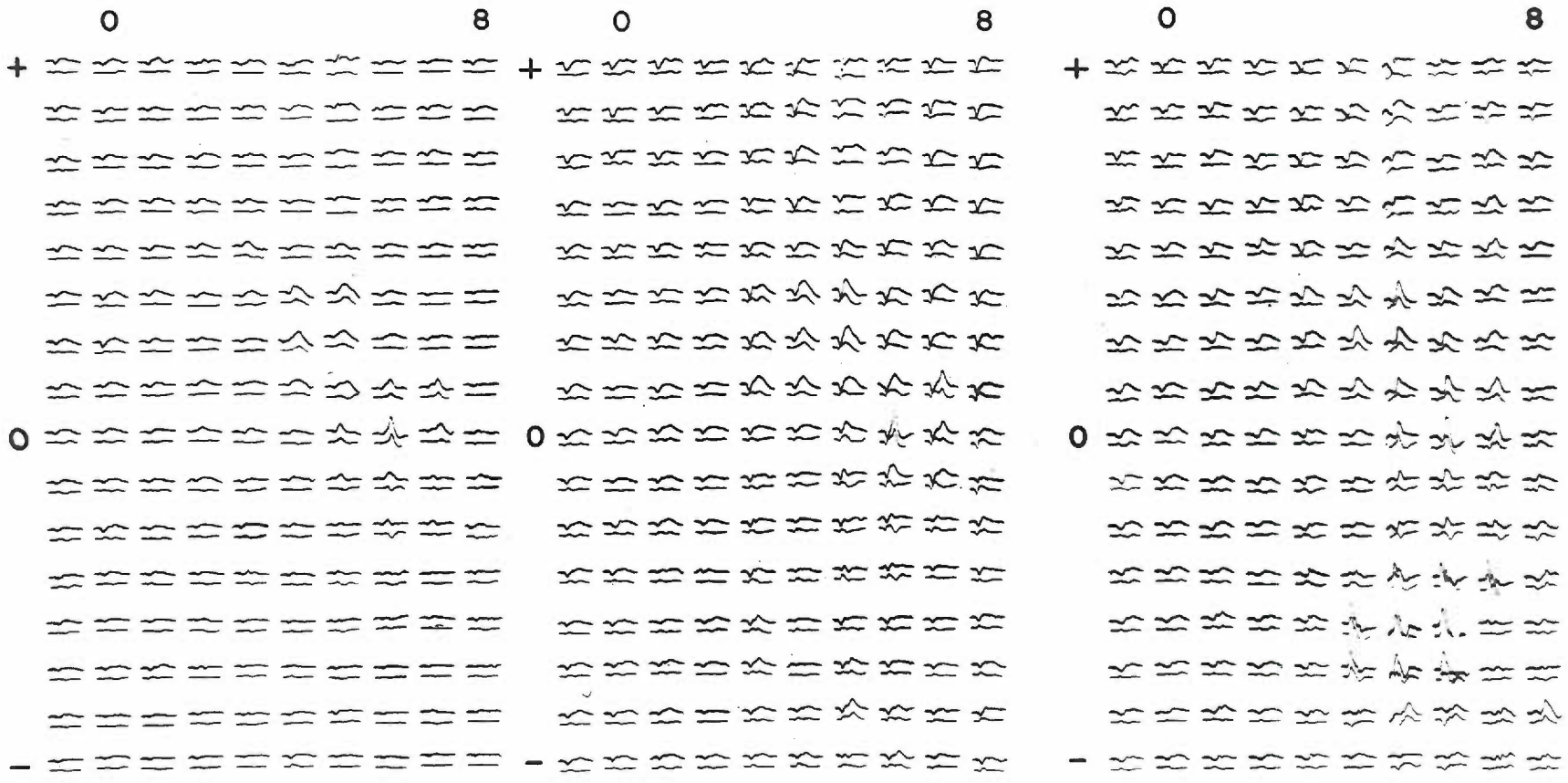


FIGURE 10

Thalamic association response map of frontal plane 12.

Optic tract responses are noted, on the visual map, 3 to 5 mm. below DV zero on ML 4 through 6. An association response field is found on ML 4 and 5, extending dorsally from the zero plane approximately 3 mm. This is the anatomic location of ventralis anterior. A more ventral association field found 6 and 7 mm. lateral to the midline corresponds to an area of the internal capsule.



SHOCK TO IPSILATERAL FOREPAW

CLICK

LIGHT FLASH

1mv

50msec

FRONTAL 12.0

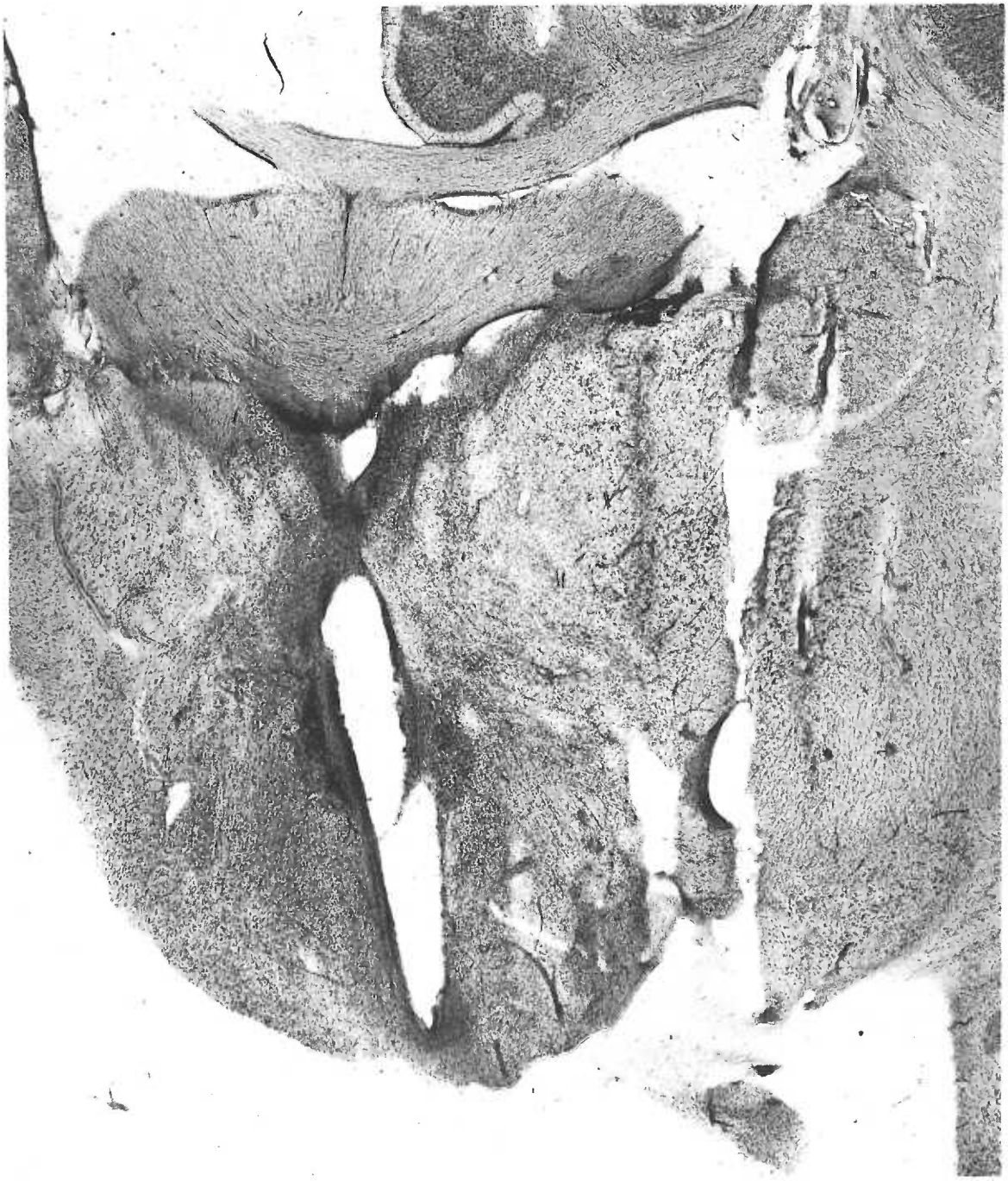
UPPER TRACE MONOPOLAR

LOWER TRACE BIPOLAR

FIGURE 11

Thalamic tissue section corresponding to response map in Figure 10. Section is at the level of frontal plane 12.

The cellular mass of ventralis anterior, with an electrode penetration track through it, is visible.



DISCUSSION

This investigation has been primarily an attempt to localize areas of the cat thalamus in which responses similar to cortical "association" responses are found. The thalamus was systematically explored until responsive fields were located. These areas were then mapped in detail. A number of problems were encountered in the course of these experiments. The paramount difficulty revolved about the extreme liability of responsiveness in the association system. Many cats were explored in which only one or two of the three modalities were reactive. Response to auditory stimulation was most often absent, even though a primary auditory response could be detected both on the ectosylvian gyrus and in the medial geniculate. Visual responses were next most likely not to be present, and evoked potentials to somatic sensory stimulation were present in most cases. Abrahams, Hilton, and Malcolm, in their study of responses in the hypothalamus, similarly report auditory potentials in only eight of twenty cats (1). It is also interesting that, as a trimodally respondent cat begins to die, the auditory response is usually the first to disappear, visual next, and tactile last.

Certain aspects of the chloralose anesthetic mechanism have recently been studied by Meulders, et. al. (36). They report maximal amplitudes of somesthetic responses, with their electrode, in centre median to be 290 microvolts (SD=83 microvolts) in the locally anesthetized, cortically intact cat. One half hour post injection of chloralose (80 mg/kg.), the maximal response at the same recording point was 550 microvolts (an augmentation of 80-100%). In waking

cats with wide telencephalic ablations, they found maximal responses of 550 microvolts (SD=82.5), which were not augmented by chloralose administration. Meulders, et. al. concluded that chloralose "removes a controlling mechanism of telencephalic origin which is normally responsible for the small amplitudes of evoked potentials in centre median seen in the awake animal."

It has been noted in the course of this study that administration of a sustaining dose of chloralose to a "light" animal has enhanced the evoked thalamic potential on several occasions. It should be pointed out, however, that initial overdosage with chloralose is often associated with a poorly responding animal.

Concurrent with the present investigation, pertinent research by others has corroborated certain of the findings presented here. Albe-Fessard, Bowsher, and Mallart (3) have also found responses to diverse somatic stimulation in the reticular formation. They have electrically stimulated in the reticular formation (the giganto-cellular nucleus of Olszewski), and recorded short latency responses in centre median. Local cooling of the reticular formation was found to selectively block CM responses to peripheral stimulation. They concluded that somatic sensory input to the reticular formation is relayed anteriorly to centre median. Auditory and visual modalities, however, were not investigated at that time, regarding reticular input or cephalic transmission. Also, centre median is the sole thalamic structure related, by this group, to the subcortical association system (3, 5, 29, 36).

An excellent study investigating hypothalamic responses to peripheral cutaneous, auditory, and visual stimuli in the chloralose-anesthetized cat was recently done by Abrahams, Hilton, and Malcolm (1). These authors found electropositive potentials of relatively long latency in widespread areas of the hypothalamus, central gray, and midbrain tegmentum. The responses they describe are similar in appearance, latency, and location elicited to responses found in the present investigation. They described both intrasensory and intersensory convergence upon these structures. Illumination of small, widely separated areas of the retina evoked potentials, at a single recording site, similar to those produced by widely separated cutaneous stimulation. Interaction studies, similar to the techniques described in the first section of this paper, again indicated intersensory convergence.

Abrahams, et. al., found survival of the described mid-brain response to somesthetic stimulation, following high decerebration, in all four cats studied.[3] Auditory responses were present in only one of the four animals, and visual responses were found in none of them. In another series of five acute cats (under chloralose), evoked potentials to cutaneous stimulation remained following pericruciate and anterior orbitofrontal cortical ablation by suction. Also, visual responses were still present following removal of all occipital and striate cortex.

The three cortical lesions studied in the present investigation differed from those in the above experiments in that all areas of trigeminal association cortex, but only association cortex, was

[3] "...decerebration was performed at a high level with the intention of removing most of the brain lying dorsal and anterior to the hypothalamus."

removed. Another most important difference is that Abrahams, et.al. studied only acute animals, whereas the present cats all had chronic lesions of at least two months duration. Unfortunately, Abrahams, Hilton and Malcolm did not specifically mention the presence or absence of auditory potentials in their decorticate cats. This is important because in the chronic cats studied here, tactile and visual responses were seen in the reticulothalamic system, but auditory potentials were found in only one cat. These were confined to a small area of the reticular formation and were of much diminished amplitude. Visual responses in these cats, although present, were also somewhat diminished in amplitude. Although this is not mentioned in their text, Abrahams, et. al. indicate the same phenomenon in their illustration of a response at a single recording site, before and after decortication (Figure 8 in reference 1).

Buser, Borenstein, and Bruner (9), in their 1959 study, concluded that the cortical association areas responding to visual and auditory stimulation are distinct from each other. They found two reactive suprasylvian areas, each composed of an auditory field and a visual field. This proposal has been contradicted by more recent work demonstrating the equivalent responsiveness of these areas to three modalities (7, 50). Buser himself has since found polyvalent single units in the pericruciate area (10). Buser, et. al. also concluded that separate areas of the lateral posterior thalamic nuclear group were responsive to auditory and visual stimulation, but that other responsive thalamic areas are modality-specific. He concluded that the visual thalamic association area occupied the

posterior nucleus and the dorsal part of the lateral posterior nucleus. The corresponding auditory areas were claimed to be located in the inferior part of the lateral posterior and the suprageniculate nuclei.

Evidence presented in this paper is contradictory to the above findings. It was found, in these experiments, that regions of the thalamus exhibiting the association response are trimodal and equivalent for auditory, visual, and somatic sensory stimulation. In addition, the posterior and lateral posterior nuclei were found to be unresponsive. The suprageniculate nucleus was reactive, but to all three modalities utilized.

Buser, et. al., in the study cited above, also found that mesencephalic reticular destruction did not abolish cortical association responses. They did not report changes in thalamic responsiveness following reticular destruction. It was found, in the single reticular lesion investigated here, that thalamic and cortical responses to auditory and tactile, but not visual, stimulation were abolished. The continuing presence of the visual response is probably explained by the fact that the lesion was made at frontal plane 2, which left intact areas of reticular formation anterior to this level. Tactile and auditory central input occur posterior to this plane, while visual input is from areas anterior to plane 2. Albe-Fessard, Bowsher, and Mallart (3), however, report abolition of somesthetic responses in centre median when certain areas of the reticular formation are compromised. Buser (9) points out that, following reticular coagulation, a transient aresponsive period follows. Although a two hour time lapse following coagulation was

permitted, the cat studied here could still possibly have been in a refractory stage. Further study of reticular lesion animals is planned.

The relationship of the thalamic system described in this paper to the cortical association system has been pointed out. Correlation and interaction data imply that the two comprise a single functional unit.

The thalamic structures which form this unit are also structures involved in the "recruiting" system (11, 14, 38). Starzl and Magoun in 1951 (46) pointed out not only that the recruiting nuclei act as a unit, but that the cortical projections of these structures is relatively specific for the frontal, cingulate, orbital, parietal, and occipital association regions. There exists a similarity between the areas of recruiting cortex described by Starzl and Magoun and the trimodal association areas mapped by Thompson, et. al. (50, 51). The parallel drawn between these two systems is not meant to imply a functional relationship between the recruiting and association responses, but to indicate only the anatomic similarity of the two thalamocortical systems. The characteristics of the recruiting response differ completely from those of the association response. Further, recruiting is only seen when the thalamus is artificially stimulated at a critical frequency range.

Data has been presented here and elsewhere (3) which implicates the reticular formation with the association system. Starzl, Taylor, and Magoun (47) have suggested both an intrathalamic and extrathalamic reticulocortical route for EEG desynchronization. The

suggested intrathalamic path involved centre median, the ventromedial and ventrolateral nuclei, the lateral wing of the intralaminar nuclei, and ventralis anterior. Again, many of these structures correspond to elements of the association system.

The extrathalamic route suggested by Starzl et. al. was from reticular formation, through hypothalamus, subthalamus, and internal capsule to cortex. Evidence is presented here, and by Abrahams et. al. (1) indicating that these regions are related to the association system.

Until quite recently, each of these areas has represented a separate field of research. It now appears that the cortical and thalamic association areas are intimately involved with the recruiting areas, the reticular formation, and both the intrathalamic and extrathalamic EEG desynchronization pathways. The association activity found in the cerebral peduncles probably represents the corticofugal discharges first described by Adrian and Moruzzi (2). This may imply a close relationship between cortical association responses and the "pyramidal" activity reported by these latter authors.

The significance of the reactivity found in the hippocampus and amygdala is, as yet, unclear.

Diminished subcortical activity following ablation of the cortical association fields may indicate a functional retrograde degeneration. Anatomic degenerative changes of a minor nature have been documented (40), but the bulk of the structure may remain intact by virtue of sustaining fibres from other areas.

The evidence obtained from the reticular lesion animal is, as yet, inconclusive and warrants no speculation.

Suggestions for further research should include:

1) A complete study of cortical and reticular lesion animals
2) A study of the effect of thalamic association area lesions
3) Hippocampal and amygdaloid mapping
4) A complete study of subcortical stimulation and recording in the involved areas.
5) A study of the relationships between the relayed pyramidal response and the association response.

SUMMARY AND CONCLUSIONS

On the cat cerebral cortex, four bilateral "association" fields have been defined electrophysiologically. The potential evoked in these areas by peripheral somatic sensory, auditory, and visual stimulation are characteristic and identifiable as a group, but indistinguishable from each other. It has been suggested that the corticopetal transmission of these potentials involves certain areas of the thalamus. The present study is an attempt to identify and map some of the diencephalic association response fields.

Electrophysiological exploration of the diencephalon with respect to potentials evoked by peripheral somatic sensory, auditory, and visual stimulation was done in forty-five cats.

Diencephalic association responses were found to correlate with cortical association responses with a Pearson product-moment coefficient of 0.94.

The intrathalamic response fields include the suprageniculate nucleus, the centre median nucleus, the ventral anterior nucleus, the rostral pole of the reticular nucleus, and the central grey area.

Responsive extrathalamic regions include the mesencephalic reticular formation, the hypothalamus, the cerebral peduncle, the hippocampus, the dorsal subthalamus, and the anterior limb of the internal capsule.

A preliminary investigation into the effects of cortical and reticular lesions on the responsiveness of these areas indicates that both have an inhibitory effect.

There is an anatomic similarity between the subcortical association structures, the elements composing the "recruiting" system, and the regions involved in reticulocortical transmission of EEG desynchronization.

The principle conclusion is that these responsive subcortical regions constitute a functional unit and that a peripheral stimulus of any modality activates this central association system in an undifferentiated manner. This system projects in an equivalent fashion to the same four cortical fields.

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