

DIFFUSE THALAMIC PROJECTION SYSTEM IN MONKEY

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IN 1942, Dempsey and Morison (4-6, 24) discovered in cats a thalamic system which upon direct repetitive stimulation evoked recruiting wave responses in broad areas of the cortex. Evidence was presented that the physiological counterpart of this response to stimulation was burst or spindle activity recorded from the cortex of cats under surgical barbiturate anesthesia. Interest in the mechanism of the recruiting response has been heightened by proposals concerning its functional significance, the most discussed being Jasper's suggestion that it represents the basis for petit mal epilepsy (15, 17, 18).

In the cat, sites of origin for the diffuse thalamic projection system have been found to be the centre median and intralaminar nuclei (24), as well as the ventralis anterior and rostral pole of the reticular nucleus (33). These component nuclei act as a functional unit for, on repetitive stimulation of any one of them, recruiting waves can be recorded from all (33). The mediation of recruiting to the cortex has been suggested to occur either through the reticular nucleus throughout its extent (17, 30, 31) or by way of the rhinencephalon (31). It has been shown (33), however, that the principal transmission of recruitment to the cortex occurs through connections with the thalamic associational nuclei, although possibly some direct connections also exist between the recruiting nuclei of origin and the cortex. In accordance with these findings, the cortical responses were found to be limited to areas having projections from these association nuclei, with identical cortical localization irrespective of which recruiting nucleus was stimulated (33). The foregoing evidence in the cat suggested that the diffuse projection system is organized for mass thalamic influence on associational cortex (33). However, because of the relatively poor differentiation of the cat's associational nuclei and cortex, in the present study more conclusive evidence was sought in the macaque, which, with its higher order of both cortical and sub-cortical development, more closely simulates the human brain.

METHODS

Acute experiments were performed on 20 *Macaca mulatta* monkeys, anesthetized with 30-35 mg./kg. Nembutal IV. Bipolar concentric electrodes, oriented with a Horsley-Clarke apparatus, were used to stimulate or pick up from the thalamus, using a polar distance between the tip and the barrel of 1 mm. or less. To avoid the impaction of two electrode

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carriers in the study of diencephalic projections, the stimulating electrode was angled into the thalamus from the rear, while the recording electrode was placed vertically in the usual manner. Condenser discharges with a falling phase of 1 msec. and a usual frequency of 5 or 6/sec. were delivered from a Goodwin stimulator, and the recruiting responses elicited recorded with a Grass model-3 amplifier and inkwriter. For regional cortical pickups a Grass multiple electrode carrier was used with silver-balled electrodes for pial contact. But for cortical localization of the recruiting response, the more accurate bipolar concentric electrodes were used with tip penetrating into the deeper cortical layers while the barrel rested on the surface. These were manipulated through the highly mobile Grass multiple electrode carrier. For surface recording from the orbital cortex the eye was enucleated, and the roof and medial surface of the bony orbit removed. To reach the full extent of the temporal pole, the eye was taken out and the sphenoidal ridge resected. In studying insular cortex, the frontal and parietal opercula were eliminated by subpial suction; to reach the medial surface of the cortex, a portion of the opposite hemisphere was sucked out, the inferior sagittal sinus ligated, and the inferior part of the falx cerebri removed. To corroborate under more physiological conditions the results obtained from hidden cortical regions whose exposure required extensive surgery, these same areas were probed with recording electrodes oriented with a Horsley-Clarke apparatus. Shock artifact was effectively reduced by grounding both temporal muscles. All brains were worked up histologically for localization of deep electrode placements.

RESULTS

Thalamic origins of diffuse projection system. Systematic exploration of the diencephalon and upper midbrain was conducted, stimulating with a frequency of 5 or 6/sec. at each mm. level as the electrode descended. Electrocorticograms were obtained from the frontal region, and from the parietal association area (Fig. 1). The thalamic sites whose stimulation elicited recruiting responses are depicted in Figure 3 by solid triangles, while non-excitabile points are shown by dots. Responsive regions included, anteroposteriorly, the cephalic pole of the reticular nucleus (Fig. 3A), the ventralis anterior (B, C) a group of adjacent midline nuclei (B), centralis medialis and lateralis (C), the lower part of the medial nucleus (C-E), centre median (D, E), and the parafascicularis nucleus (E). The rostral portion of the centre median, which lies in medial relation to the ventralis posterior somatic relay group, was curiously silent, recruiting responses being obtained only from stimulation along its upper margin (D), but the caudal extremity of this nucleus was strongly positive (E). Examples of the cortical recordings obtained during stimulation of various excitable nuclei are shown (Fig. 1) from rostral pole of the reticular nucleus (A), ventralis anterior (B), centralis medialis (C), inferior part of the medial nucleus (D), and the centre median (E). The cortical activity provoked by stimulating anywhere in this thalamic zone—of approximately 8 mm. rostrocaudal extent—was essentially the same, consisting of high amplitude waves with a greater or lesser recruiting tendency. The optimum frequency for stimulation was 6/sec. (Fig. 2A-1), a rate as low as 3/sec. yielding poor effects (A-2), and 10/sec. producing only slight changes in background activity (A-3). The threshold for recruiting varied from 1 to 4 volts, routinely being considerably lower in the cephalic end of the system, especially in the ventralis anterior.

In addition to the pure waves described, a variant of the recruiting response was often noted with stimulation of the medial nucleus, in which

spikes were interposed amongst the evoked waves. These complex effects assumed many forms, the spike sometimes coming in with the initial shock, being submerged in the developing waves with the succeeding stimuli, and finally reappearing (Fig. 2B-1). At other times the spike component underwent a voltage increment with the accompanying wave (B-2). In these instances, effects were also found in the parietal association area (B), far re-

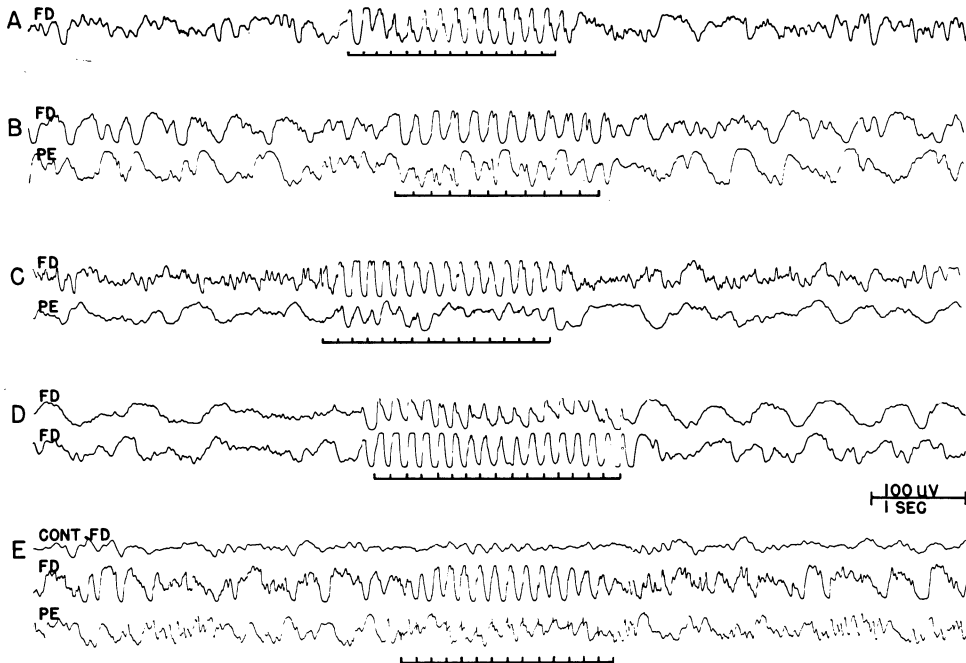


FIG. 1. Cortical recruiting responses obtained with stimulation of nuclei of origin of diffuse thalamic projection system—rostral pole of reticular nucleus (A), ventralis anterior (B), centralis medialis (C), inferior part of medial nucleus (D), and centre median (E). Cortical nomenclature is: FD—frontal association cortex (Walker-Brodman area 8, 9 or 10); Cont. FD—contralateral frontal association cortex; PE—parietal association cortex (Brodman area 39, 19 or 7). Repetitive stimulation was at 5 or 6/sec., and stimulating voltages between 5 and 7.

moved from the known projection cortex of the medial nucleus. The generality of these evoked waves renders it likely that at least part of the medial nucleus represents an integral portion of the diffuse projection system, especially since stimulation of its inferior part often evokes pure recruiting wave potentials. The rest of the thalamus was always explored, but recruiting responses were never evoked elsewhere than in the regions indicated. With stimulation of the lateralis posterior and pulvinar, augmenting waves were recorded from the parietal cortex. However, although there was occasionally a slight increase in frontal synchrony, discrete responses were

strictly limited to the parietal area to which these nuclei are known to project (Fig. 2C).

Although the reticular thalamic nucleus was excited many times, recruiting responses could on no occasion be elicited except from its rostral pole. Likewise, the midbrain tectum and tectum, sub- and hypothalamus,

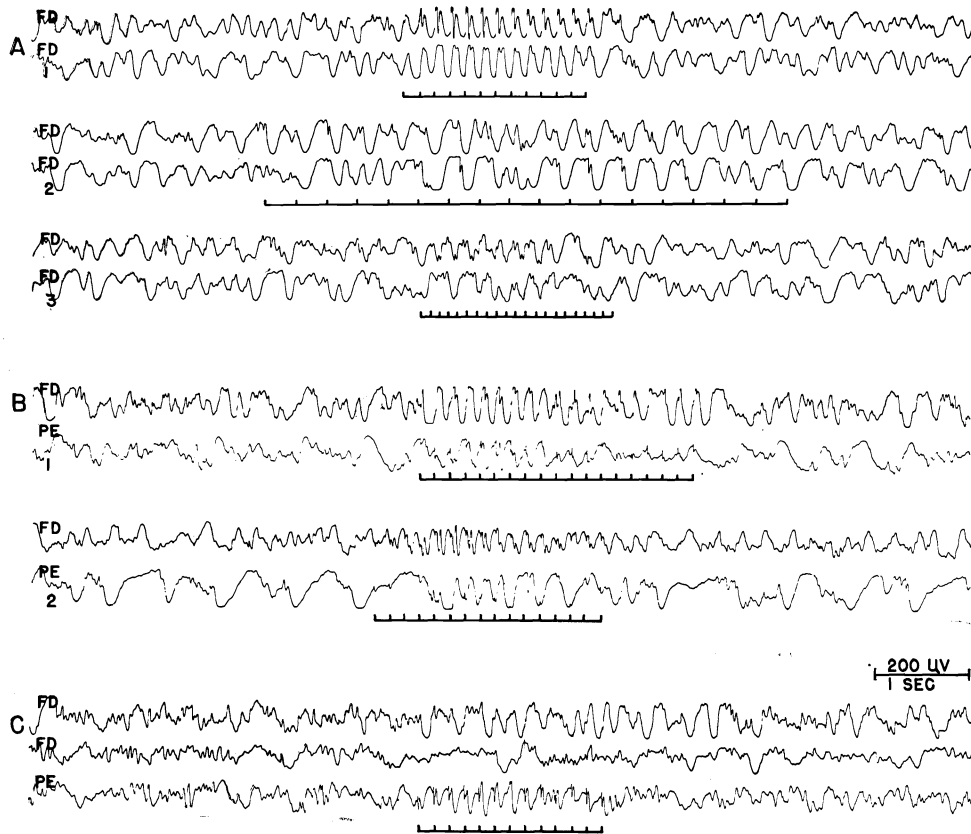


FIG. 2. Elocorticograms obtained with repetitive thalamic stimulation. A—Effect of frequency alteration on recruiting response, stimulating ventralis anterior at 6/sec.:1, 3/sec.:2, and 10/sec.:3. B—Atypical recruiting responses having prominent spike components with stimulation of medial nucleus. C—Waves, limited to parietal association cortex, evoked by stimulation of pulvinar. Cortical abbreviations are: FD—frontal association cortex; PE—parietal association cortex. Repetitive stimulation was at 6/sec. unless otherwise indicated with voltages between 5 and 7.

caudate nucleus, putamen and globus pallidus were all unresponsive to direct low frequency stimulation.

In general, then, the sites of origin of the diffuse thalamic projection system are the same as those previously reported in the cat (24, 33). This medially located thalamic system consists of the parafascicularis, centre median, intralaminar nuclei, inferior part of the medial nucleus, ventralis

anterior, and the rostral pole of the reticular nucleus. The cephalic end of the system is the most excitable, particularly in the region of the ventralis anterior. The medial nucleus was more strongly implicated than in the cat,

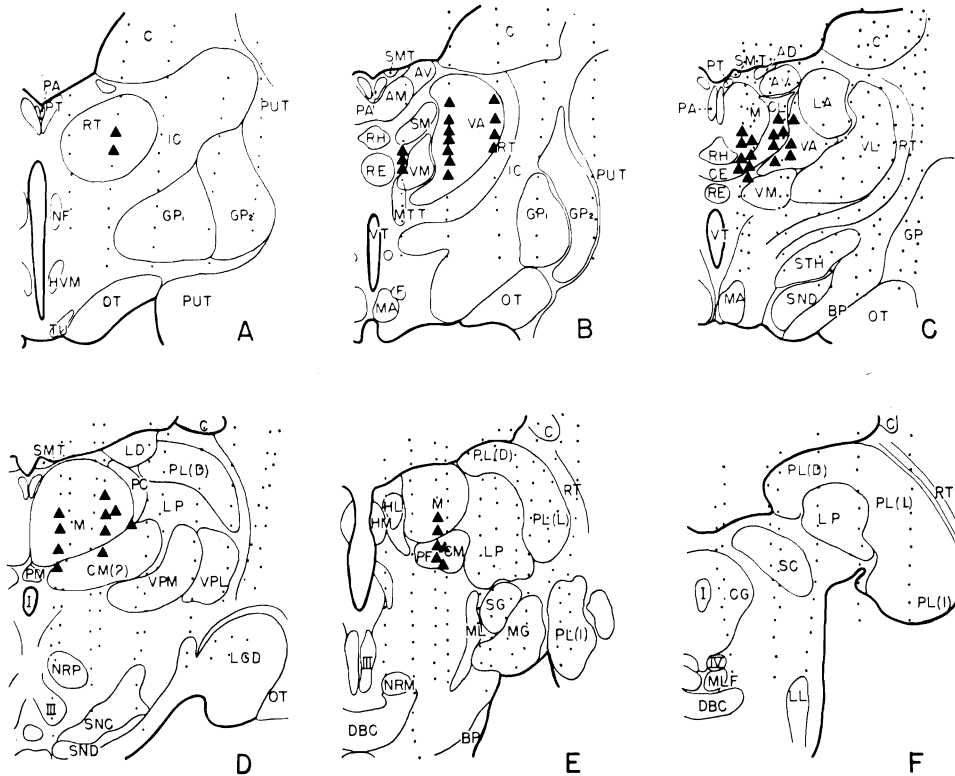


FIG. 3. Transverse sections through diencephalon and upper midbrain of macaque showing regions, indicated by solid triangles, where 6/sec. stimulation evoked cortical recruiting responses. Negative points are shown with small dots. Abbreviations are: AD- anterodorsal nuc., AM-anteromedial nuc., AV-anteroventral nuc., BP-basis pedunculi, C-caudate nuc., CE-centralis medialis, CG-central gray, CL-centralis lateralis, CM-centre median, CM-anterior part of centre median, DBC-decussation of brachium conjunctivum, F-fornix, GP₁ and GP₂-globus pallidus, HL-lateral habenular nuc., HM-median habenular nuc., HVM-ventromedial nuc. of hypothalamus, I-iter, III-oculomotor nuc. and nerve, IV-trochlear nuc., IC-internal capsule, LA-lateral anterior, LD-lateralis dorsalis, LGD-lateral geniculate dorsalis, LL-lateral lemniscus, LP-lateralis posterior, M-medial nuc., MA-mamillary body, MG-medial geniculate, ML-medial lemniscus, MLF-medial longitudinal fasciculus, MTT-mamillothalamic tract, MF-filiform nuc., NRM-large-celled part of red nuc., NRP-small-celled part of red nuc., OT-optic tract, PA-paraventricular nuc., PC-paracentralis, PF-parafascicularis, PL(D)-dorsal pulvinar, PL(I)-inferior pulvinar, PL(L)-lateral pulvinar, PM-paramedian nuc., PT-parataenial nuc., PUT-putamen, RE-reuniens, RN-rhomboid nuc., RT-reticular nuc., SC-superior colliculus, SC-suprageniculate nuc., SMT-olfactohabenular stria, SNC-substantia nigra compacta, SND-substantia nigra diffusa, STH-subthalamic nuc., VA-ventralis anterior, VL-ventralis lateralis, VM-ventromedial nuc., VFL-ventroposterolateral nuc., VPM-ventroposteromedial nuc., VT-third ventricle.

which, as subsequent data will further indicate, may be related to increased frontal specialization in the monkey.

The *subcortical projections of the diffuse thalamic system* were studied by recording in deeply located areas during repetitive stimulation of the recruiting nuclei of origin. Responses, wherever found, manifested common characteristics. The evoked potentials were always waves, usually recruiting

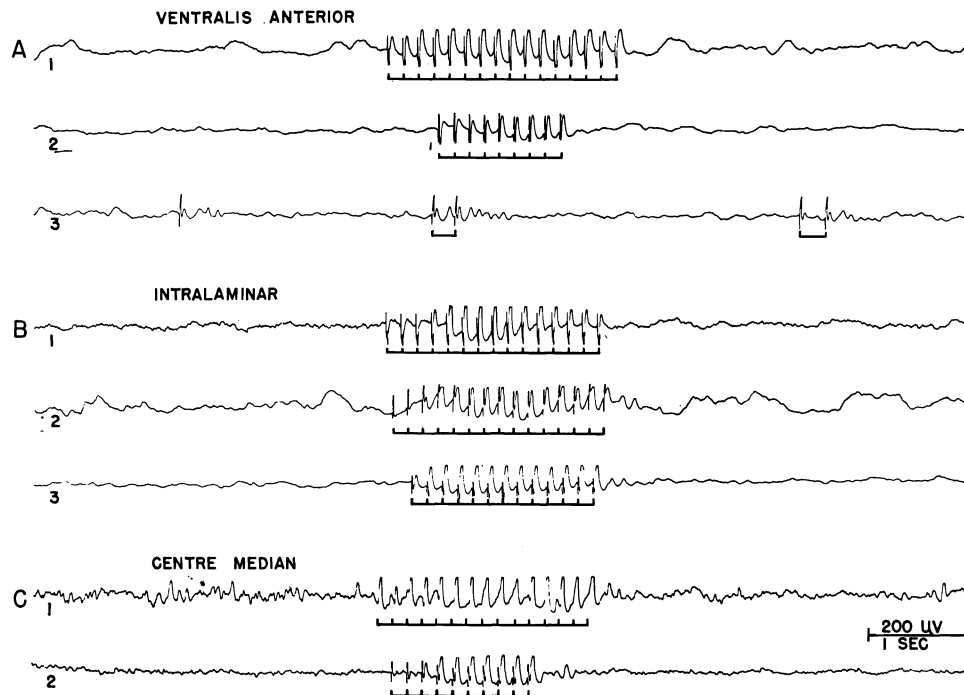


FIG. 4. Records illustrating intrathalamic conduction of recruiting responses between nuclei of origin of diffuse projection system. In A are recruiting waves recorded from ventralis anterior during repetitive stimulation of centralis lateralis: 1, and centre median: 2, as well as spindle activity precipitated by single or double shocks to the centralis lateralis: 3. Responses are shown in the intralaminar nuclei (B), stimulating the ventralis anterior and recording from the centralis lateralis: 1, stimulating the centralis lateralis and recording from the centralis medialis: 2, and stimulating the centre median and recording from the centralis lateralis: 3. In C are records from centre median during stimulation of ventralis anterior: 1, and centralis lateralis: 2. Repetitive stimulation was at 6/sec., and stimulating voltages between 3 and 7.

(Figs. 4, 5), which made the problem of distinguishing response from shock artifact an easy one. Phase reversal of the potentials as the electrode passed through the responsive zone was often seen, as illustrated from the medial (Fig. 5A) and ventromedial (B) nuclei, and from the pulvinar (E).

In the thalamus, localization of responses was essentially the same no matter which of the diffuse thalamic nuclei was stimulated. Thus in Figure 6 recruiting potentials could be obtained from all the shaded zones upon stimu-

lation of any one of the sites marked with vertical dumb-bells. Responsive areas included all of the recruiting nuclei of origin just outlined by stimulation, and most of the thalamic association nuclei as well.

In the recruiting nuclei of origin, the most significant finding was their mass excitation. With stimulation of the front of the system, the waves were

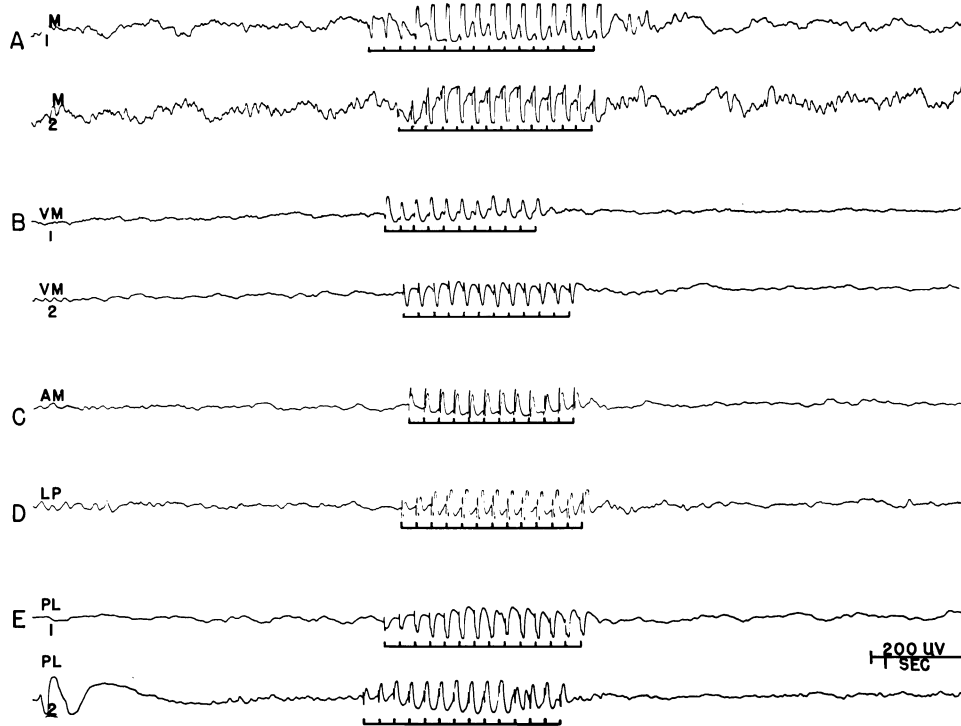


FIG. 5. Records illustrating intrathalamic conduction to association nuclei upon stimulation of diffuse nuclei of origin. Pickups were from medial nucleus (A) during stimulation of ventralis anterior; ventromedial (B) and anteromedial (C) nuclei during stimulation of centre median; lateral posterior (D) with stimulation of centralis lateralis; and pulvinar (E) with stimulation of ventralis anterior. Examples are seen (A, B, E) of phase reversal commonly encountered in passing through a responsive recording zone. Stimulation was at 6/sec. with voltages between 3 and 7.

propagated to the posterior diffuse nuclei; with excitation in the middle, potentials passed both rostrally and caudally; and on stimulation of the rear of the system, a sweep of waves occurred forward to the cephalic diffuse nuclei. Thus the responsive areas in all cases included the rostral pole of the reticular nucleus (Fig. 6A), ventralis anterior (B, C), centralis medialis (C, D), centralis lateralis (C-E), inferior part of the medial nucleus (C-E) and centre median (D, E). Illustrated are examples of this intrathalamic conduction between the different recruiting nuclei (Fig. 4). Recordings are shown from the ventralis anterior (A) during stimulation of the centralis

lateralis (A-1) and centre median (A-2); from the intralaminar nuclei (B) during stimulation of the ventralis anterior (B-1), centralis lateralis portion of the intralaminar complex (B-2), and centre median (B-3); from the centre median (C) with stimulation of the ventralis anterior (C-1) and centralis lateralis (C-2). It is interesting to note that when the pickup is taken from the same nucleus that is being stimulated, typical recruiting responses can be recorded, indicating that wave production occurs even at an intranuclear level (Fig. 4B-2). In the instance shown, the stimulus and pickup were in the centralis lateralis and centralis medialis respectively, which are merely anatomical subdivisions of the same nuclear mass. Similar intranuclear effects have been reported in the cat for other diffuse nuclei, particularly the ventralis anterior (33).*

In addition to this intrathalamic conduction through the recruiting nuclei, strong connections were also demonstrated to the association nuclei. These included anteromedial and anteroventral nuclei (Fig. 6B), medial nucleus through its entire extent (C-E), lateralis anterior (D), lateralis posterior (D-F) and pulvinar (E-F). Also implicated in the perimeter of the responsive zone were some of the midline nuclei (B), and the dorsal tip of the ventromedial nucleus (C) whose function and connections are not known. Examples from these areas are shown (Fig. 5), from the medial nucleus with stimulation of the ventralis anterior (A); the ventromedial nucleus with stimulation of the centre median (B); anteromedial nucleus with stimulation of the centre median (C); lateralis posterior with stimulation of the centralis lateralis (D); and from the pulvinar with stimulation of the ventralis anterior (E).

The medial nucleus seems to enjoy a unique position among the nuclei of origin of the diffuse thalamic projection system, and the association nuclei to which they project. The results of stimulation (Fig. 3C-E) revealed that typical recruiting responses could be obtained by excitation of its inferior portion. This in itself is of interest since, although the other diffuse nuclei fail to exhibit retrograde degeneration with cortical ablation, the medial nucleus with its strong rostral radiations undergoes extensive chromatolytic changes with extirpation of the orbitofrontal association cortex. For this reason, it has been considered an association nucleus and as such is the only nucleus of this classification whose stimulation will elicit cortical recruiting responses. From the study of intrathalamic conduction of recruiting potentials, it was similarly seen that evoked waves could be recorded from broad portions of the medial nucleus, the positive zone being much

* In addition to the results of repetitive stimulation, trains of wave activity could often be precipitated in one of the recruiting nuclei by single or double shocks delivered to other diffuse nuclei (Fig. 4A-3). It was impossible, however, under the conditions of these experiments to make comparisons between the distribution of this spindle tripping effect, spontaneous bursts, and the recruiting response, since spontaneous bursts were not a usual feature of the background in either cortical or deep pickups. This was presumably because the required surgical level of barbiturate anesthesia was inappropriate for this kind of spontaneous activity.

larger (Fig. 6C-E) than the part outlined as excitable with direct stimulation. In short, the medial nucleus appears to play a dual role in the mechanism of the recruiting response—its inferior segment being an integral part of the central core involved in the production of the potentials, while

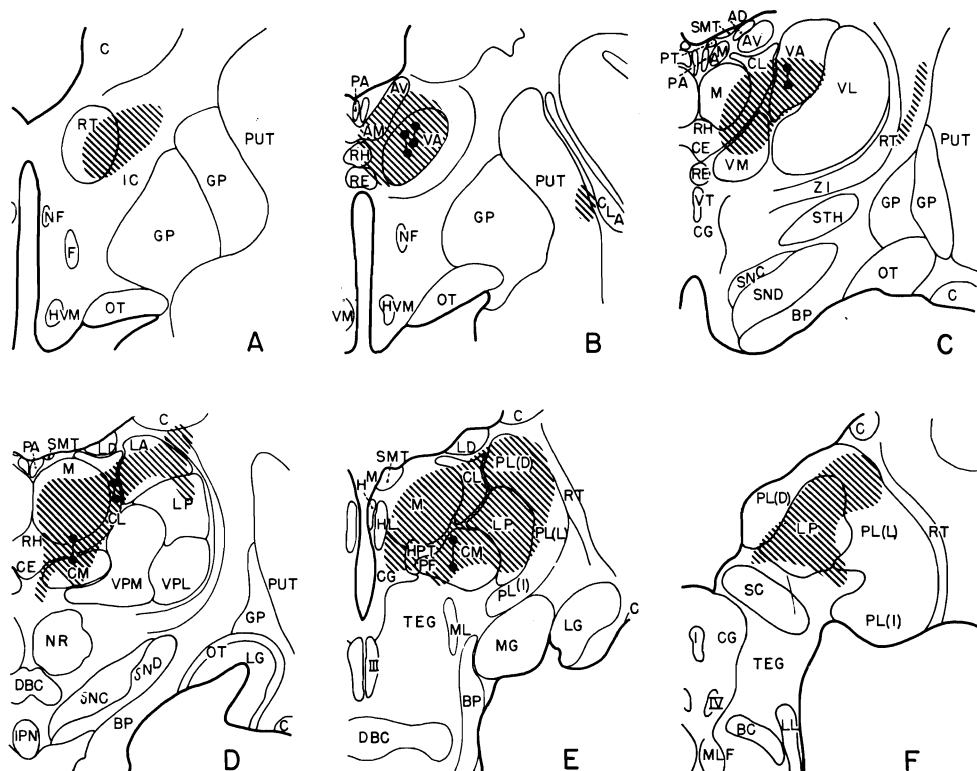


FIG. 6. Transverse sections of diencephalon and upper midbrain of macaque, showing regions from which recruiting responses could be recorded during stimulation of diffuse thalamic nuclei of origin. Localization of tip and barrel of stimulating electrode is indicated by solid balls connected with bar, and areas of response are shown by shading. Projection areas were identical no matter which of recruiting nuclei of origin was stimulated. Abbreviations are: AD-anterodorsal nuc., C-caudate nuc., CE-centralis medialis, CG-central gray, CL-centralis lateralis, CLA-claustrum, CM-centre median, DBC-decussation of brachium conjunctivum, F-fornix, GP-globus pallidus, HL-lateral habenular nuc., HM-medial habenular nuc., HPT-habenulopeduncular tract, HVM-ventromedial nuc. of hypothalamus, I-iter, III-oculomotor nuc., IV-trochlear nuc., IC-internal capsule, IPN-interpeduncular nuc., LA-lateralis anterior, LD-lateralis dorsalis, LG-lateral geniculate, LL-lateral lemniscus, LP-lateralis posterior, M-medial nuc., MG-medial geniculate, ML-medial lemniscus, MLF-medial longitudinal fasciculus, NF-filiform nuc., NR-red nuc., OT-optic tract, PA-paraventricular nuc., PF-parafascicularis, PL(D)-dorsal pulvinar, PL(I)-inferior pulvinar, PL(L)-lateral pulvinar, PUT-putamen, RE-reuniens, RH-rhomboid nuc., RT-reticular nuc., SC-superior colliculus, SMT-olfactohabenular stria, SNC-substantia nigra compacta, SND-substantia nigra diffusa, STH-subthalamic nuc., TEG-midbrain tegmentum, VA-ventralis anterior, VL-ventralis lateralis, VM-ventromedial nuc., VPL-ventroposterolateral nuc., VPM-ventroposteromedial nuc., VT-third ventricle.

the more dorsal portions receive intrathalamic connections in the same manner as the other thalamic association nuclei.

These intrathalamic projections were delineated with far greater clarity in the present work than had been possible in the cat (33) due to the greater size of the thalamus, further specialization of the association nuclei, and the relative isolation of the relay nuclei. Although thoroughly explored on many occasions, no recruiting responses could ever be found in the ventralis posterior or medial and lateral geniculates, nor was there any evidence of connections to the ventralis lateralis, the cerebello-thalamo-cortical relay station. Similarly the reticular nucleus was completely silent except for its rostral pole. It has been impossible, therefore, with both stimulating and recording techniques, to furnish the slightest evidence for the concept (17, 30, 31) that the extent of the reticular nucleus is involved in the mechanism of the recruiting response, either in its production or mediation.

In summary, the nuclear origins of the diffuse thalamic projection system have rich reciprocal interconnections, forming in total a functional unit capable of complete excitation upon stimulation of any of its constituent parts. Corticopetal impulses from this neural mass appear to be mediated chiefly through the thalamic association nuclei although possibly some direct connections with the cortex also exist. The mass discharge within the system allows easy understanding of the identical projections from its component parts, and places it in key position to influence large cortical areas through the associational nuclei.

Within the basal ganglia, the head of the caudate nucleus exhibited recruiting potentials upon thalamic stimulation, but these were more capricious than in the cat. The globus pallidus never responded. In one case, responses were found in the junction between the putamen and claustrum (Fig. 6B) but in general these structures were negative. Strong recruiting responses have been reported in the cat's claustrum but, as was pointed out, only in areas subjacent to the orbital cortical projection focus (33). The internal capsule was relatively silent, only occasional small effects being seen (Fig. 6A, C). No responses were ever recorded in the midbrain tectum or tegmentum, or in the sub- or hypothalamus.

The *cortical projections of the diffuse thalamic system* were studied by repetitively stimulating the various nuclei of origin and plotting the surface distribution of recruiting responses. The best localization was possible with the use of bipolar concentric electrodes, with the tip placed into the deeper strata of the cortex and the barrel resting on the surface. The areas outlined in this way were checked with the standard bipolar surface pickup method. Paralleling the findings in the thalamus, the distribution of these cortical potentials was found to be identical no matter which of the diffuse nuclei was stimulated.

There was considerable variation in the response, in both form and amplitude. The most intense and reliable effects were always frontally located, parietal or occipital recruiting being smaller (Fig. 7C) and often imperfectly

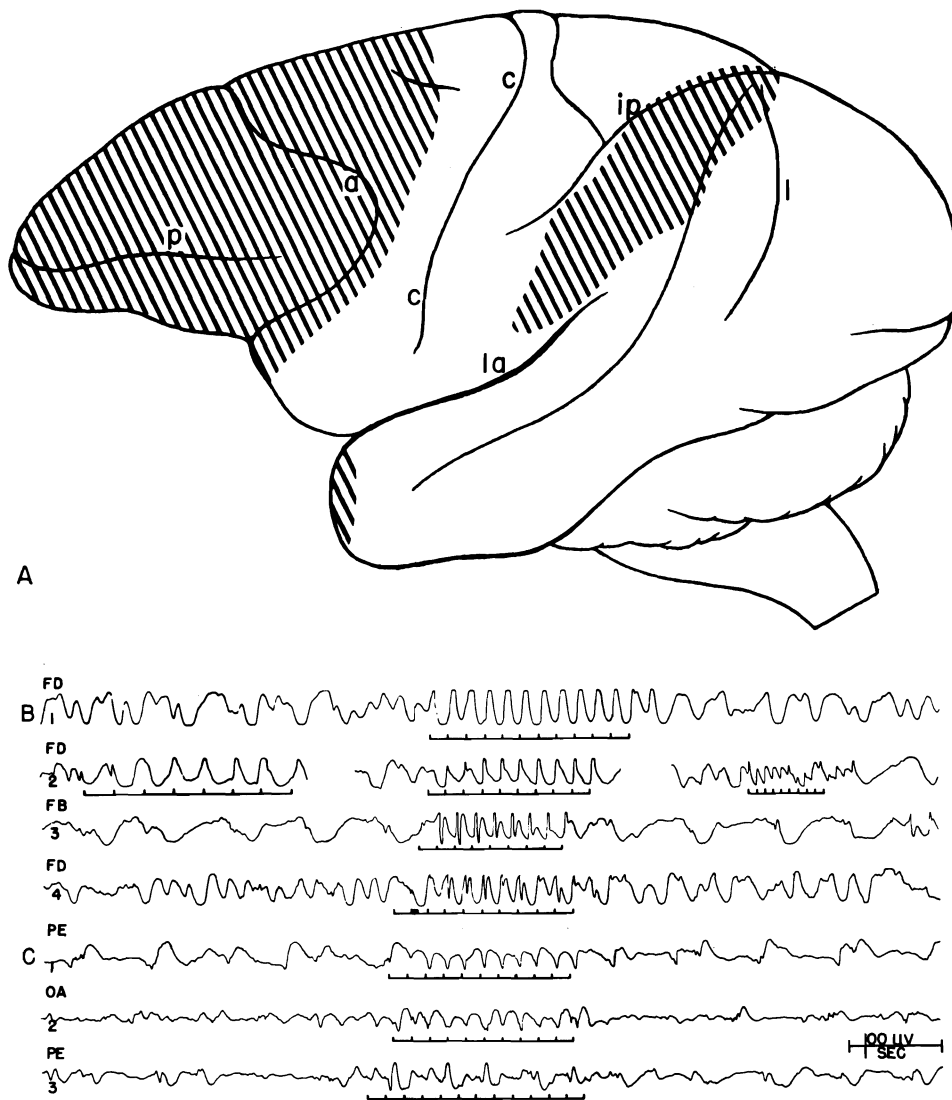


FIG. 7. Study of diffuse thalamic projections on dorsolateral cortex of macaque. A—Cortical projections of recruiting waves, indicated by shading. B—Recordings from frontal cortex showing variations in type of response form with different sites of pickup: 1, 3, 4 and with different frequencies of thalamic stimulation: 2. C—Recruiting responses from different places in parietal association cortex. Abbreviations on cortical map are: a—arcuate s., c—central s., ip—intraparietal s., l—lunate s., la—lateral (Sylvian) s., p—sulcus principalis. Abbreviations on electrocorticograms are: FB—dorsal premotor cortex (Area 6), FD—frontal association cortex (Area 9, 10 or 46), OA—occipital association cortex (Area 18), PE—parietal association cortex (Area 39 or 7). Stimulus frequency was 5/sec. except in B-2 where 3, 5 and 10 were used. Voltages were from 5 to 7.

following the stimulus (C-3). Changes in rate of stimulation differentially affected various cortical regions. In the frontal areas frequencies could often be followed through 3 to 10 or 12/sec. (Fig. 7B-2), but in the parietal zone all response was usually lost beyond the range of 5-7/sec. These feeble characteristics also typified contralateral recruiting responses (Fig. 1E), which were found only frontally. Wave form also exhibited great variation. Although the response was typically smooth and monophasic (Fig. 7B-1), examples were often seen of biphasic (Fig. 8B) or triphasic (Fig. 7B-3, 4) waves. These variants seemed related more to the local condition of the cortex than to the exact site of pickup, for frequently when a recording electrode was left in place for some time in the course of an experiment, the potential configuration would change several times. This is not surprising in the light of the recent evidence of Arduini and Terzuolo (1) that the cortical recruiting response consists of two components—one, highly resistant to environmental influences, is attributable to corticopetal fiber discharge; the other, easily altered by various means, is caused by discharge set up in cortical neurones.

The topography of recruiting projections on the dorsolateral cortex (Fig. 7A) shows clearly the increasing frontal specialization of this system in the macaque. The great bulk of the rostral responsive zone lies anterior to the arcuate sulcus, including the Walker-Brodman areas 8A and B, 9, 10, 12, 45 and 46. This region is considered to be frontal association cortex possessing uniform cytoarchitectural characteristics (3). The mechanism of recruitment in this area is easily understandable by virtue of its rich connections from the medial nucleus, which, as pointed out, is involved in both the production and relay of the recruiting response. In addition, there was some overlap into the premotor cortex, this being slight in the lower portion (areas 44 and 6), but becoming more extensive in the dorsal part of area 6. Although it has weak connections from the ventralis lateralis (37), the latter band of cortex probably does not display recruiting responses by mediation through this thalamic nucleus. As noted earlier (Fig. 6), no subcortical recruiting could ever be found in the ventralis lateralis. Moreover, responses were not found in cortical area 4, which is one of the principal terminations of fibers from this nucleus. A more tenable view may be that fibers from the medial nucleus reach somewhat further posteriorly than is at present thought, or—what is less likely—that there is some transcortical spread of the evoked waves. Nor can the possibility be disproved at present that this posterior extension is not due to direct fibers from the diffuse nuclei of origin.

A parietal zone (Fig. 7A) was smaller than that found frontally and included all of Brodmann's area 39, portions of 40 and 19, and tiny parts of 18, 7 and 5—all part of the parieto-occipital association cortex, with strong thalamocortical connections from the pulvinar and lateralis complex. Responsive also was the temporal tip (area 39) which has been shown by recent work in the cat (36) to have reciprocal connections with the lateralis pos-

terior nucleus. The comparison of these surface data with the findings on intrathalamic conduction is again of considerable interest, for the association nuclei projecting to these implicated cortical areas also exhibited strong connections from the recruiting nuclei of origin.

On the medial surface of the hemisphere (Fig. 8A) was found an extension of the frontal responsive regions previously described, including all of

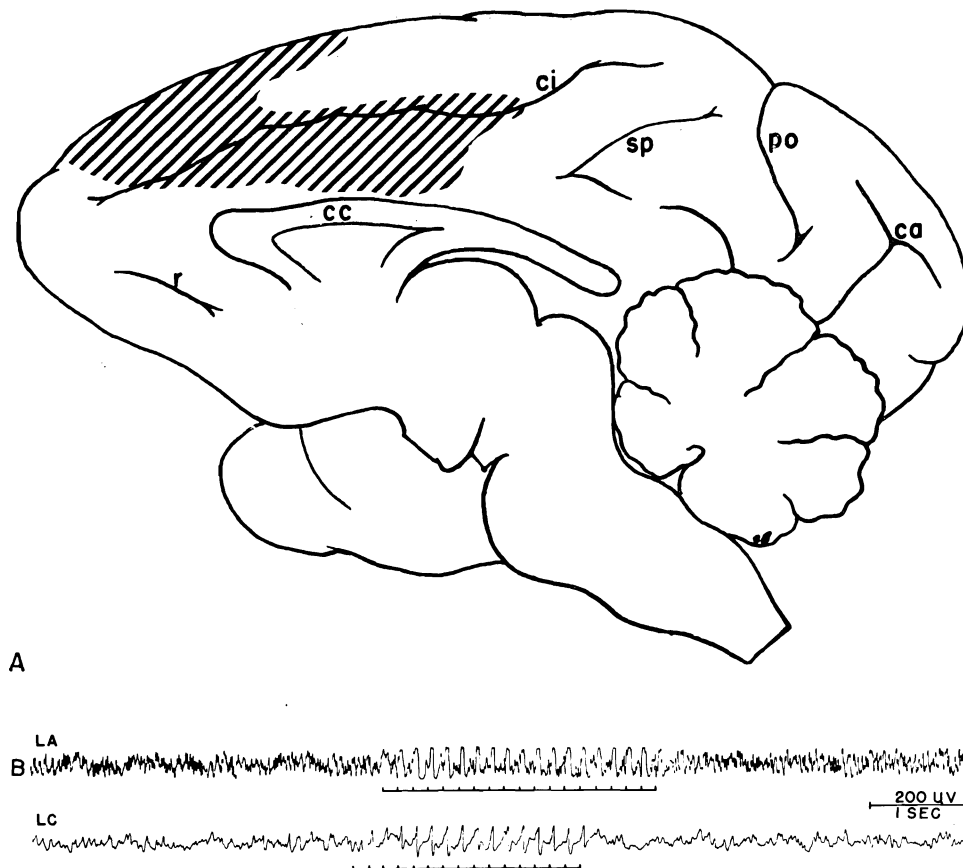


FIG. 8. Study of diffuse thalamic projection system on medial cortex of macaque. A—Cortical projections of recruiting waves indicated by shading. B—Examples of recruiting responses from rostral (LA) and caudal (LC) portions of gyrus cinguli. Abbreviations on cortical map are ca-calcarine s., cc-corpor callosum, ci-cingulate s., po-parieto-occipital s., r-rostral s., sp-subparietal s. Abbreviations on electrocorticograms are: LA-anterior cingulate (Area 24), LC-posterior cingulate (Area 24). 6/sec. stimulus frequency was employed with 5-7 volts.

Walker-Brodmann's area 9, and part of 8B and 10. From this rostral zone, the localization passed like a tongue down the anterior portion of the gyrus cinguli to involve the entire area 24. This anterior cingulate area, although formerly thought to be olfactory in nature, is now regarded as part of the

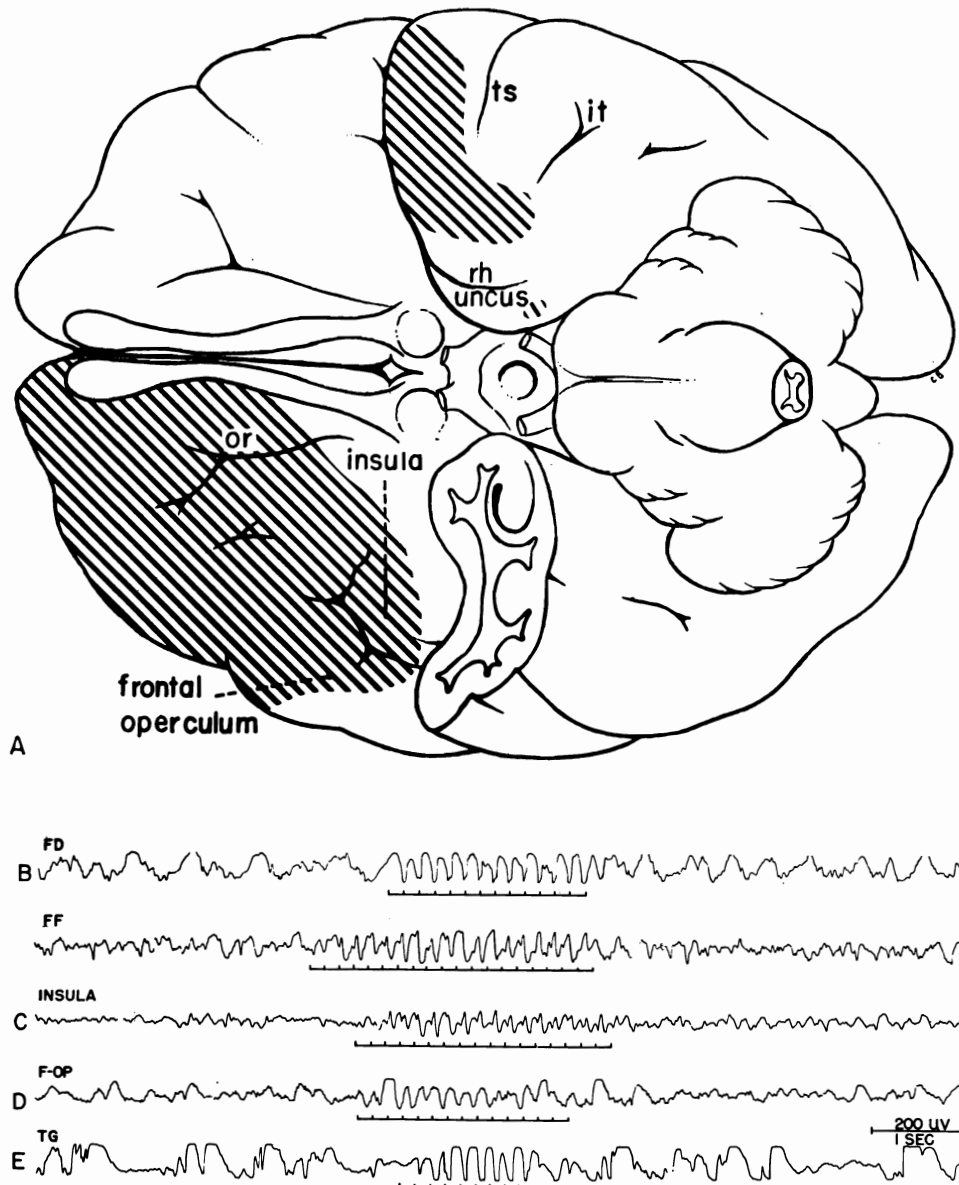


FIG. 9. Study of diffuse thalamic projection system on inferior cortex of macaque. A—Cortical projections of recruiting waves, indicated by shading. Temporal pole has been amputated on right side and stump retracted so anterior insula and frontal operculum can be seen. Temporal lobe is intact on left side. B—Records from anterior and posterior orbital cortex. C, D, E—Records from insula, frontal operculum (F-OP), and tip of temporal lobe. Abbreviations on cortical map are: it-inferior temporal s., or-orbital s., rh-rhinal s., ts-superior temporal s. Abbreviations on electrocorticograms are: FD-anterior part of orbital cortex (Brodmann-Walker area 11), FF-posterior part of orbital cortex (Walker area 13), F-OP-frontal operculum (area 44), TG-tip of temporal pole (area 38). Stimulation was at 6/sec. with voltages of 5-7.

frontal cortex. The anteromedial nucleus is known to project to it, which in the light of the intrathalamic results, again establishes the link between the recruiting nuclei of origin and the cortical projection site.

Extensive projections were also found to the inferior cortex of the hemisphere (Fig. 9A). Almost the entire orbital cortex was involved including Walker-Brodmann's areas 10, 11, 12, 13, and part of 14—all of which receive thalamocortical radiations from the medial nucleus (37). This positive zone

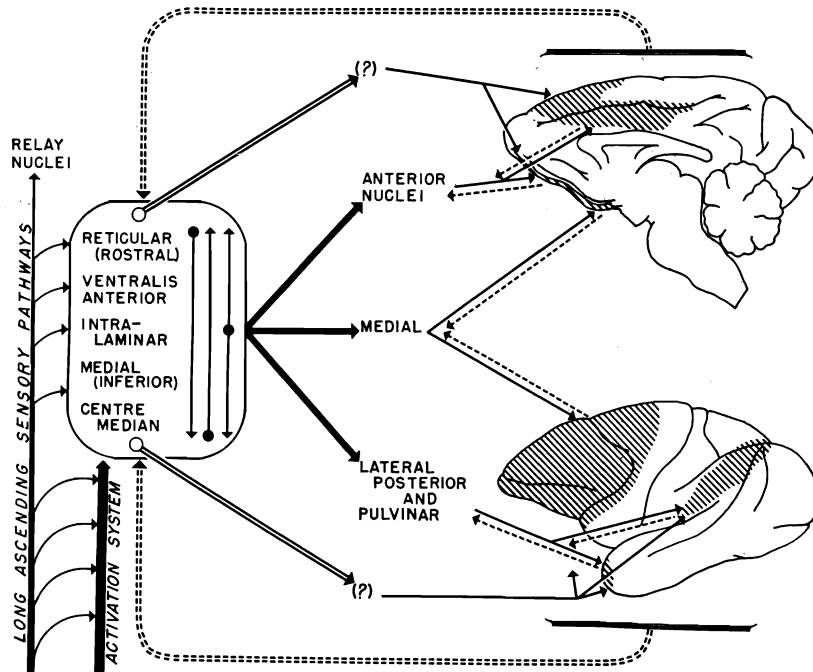


FIG. 10. Schematic representation of organization of diffuse thalamic projection system. Explanation in text.

extended back onto the frontal operculum and into the anterior part of the insula. Likewise, the tip of the temporal lobe also exhibited recruiting responses as described earlier. No effects were ever recorded from the olfactory tract or from the narrow strip of cortex medial to it (medial part of area 14). Illustrated are records from these regions (Fig. 9B-E).

In general, then, the regional topography of the recruiting system at a cortical level follows a well-defined pattern. Although the projection sites are widely distributed they all lie in association areas, each of which has connections with the thalamus—the orbitofrontal cortex from the medial nucleus, the cingulum from the anterior nuclei, and the parietal zone and tip of the temporal lobe from the nucleus lateralis or pulvinar. In turn, these association nuclei receive projections from the central nuclei of the diffuse thalamic projection system. Conversely, the cortical areas which are func-

tionally preoccupied with sensory or motor function and do not possess connections with these nuclei do not exhibit recruiting responses.

DISCUSSION

The present study of the organization of the diffuse thalamic projection system, indicates that impulses from the nuclei of origin, which discharge as a unit, are relayed to the association nuclei of the thalamus whence they pass to the associational cortex. By this mechanism the electrical activity of large portions of the cerebral mantle can be brought under control by stimulation of a very tiny area of the thalamus.

The diffuse thalamic nuclei would be placed in a curiously isolated position were it not for recent demonstrations of connections passing to them from below. In a study of auditory and somatic collaterals in the cat (34), a rich influx of fibers turning off from the main sensory pathways was described. The collateral inflow occurred to the entire region from the bulb to the basal diencephalon—the impulses from each level being propagated rostrally through the medial brain stem. Included at the rostral pole of this collateral area were the recruiting nuclei. These findings have been confirmed, and extended to the splanchnic system and visual system in the monkey (10), and similar information has been obtained for ascending cerebellar projections (39). This zone of collateralization comprises the reticular activating system (25), excitation of which causes desynchronization of electrical cortical activity such as is seen in the arousal reaction. The recruiting nuclei, included at the rostral end of this system, are thus brought under the influence of a great variety of sensory impressions—establishing for them in this way a uniquely complete liaison with the external environment.

In addition, it has been shown that many different cortical areas have connections with the recruiting nuclei of origin—demonstrated both with strychnine neuronography (27), and by thalamic exploration during local cortical after-discharge (16). By this means the diffuse thalamic nuclei can be brought into relation with events occurring at a cortical level. From this it seems that the recruiting nuclei occupy an unusually favorable position for the integration of neural activity, since they stand as common ground into which both sensory and cortical fibers discharge (Fig. 10).

The intrathalamic projections outlined in the present study offer a mechanism for ultimate widespread distribution of these incoming impulses. From the diffuse thalamic nuclei impulses pass to the various association nuclei, apparently causing discharge of their constituent neurons. It has long been known that reciprocal fiber connections existed between these association nuclei and the respective cortical association areas (12, 37), furnishing the anatomical basis for cortical subcortical reverberating circuits. But the physiological circumstances provoking activity in these pathways has remained obscure. The present findings make it clear that the thalamo-cortical portion of these association circuits can be discharged by excitation from the diffuse thalamic nuclei.

Existing knowledge of these connections of the diffuse thalamic projection system has been for the most part based on electrophysiological studies. Although the optimum frequency for direct stimulation of the diffuse nuclei is 6/sec., repetitive excitation at a comparable rate of either the cortex or collateral sensory system does not, so far as is known, cause recruiting responses. However, a single afferent stimulus (34) or the discrete impulse of a cortical strychnine spike (26) can cause in the diffuse nuclei a 6/sec. bursting discharge with many of the features of the recruiting response. This capacity for repetitive discharge would seem to impute to the recruiting nuclei a high degree of inherent rhythmicity, a feature which is hardly surprising in view of their mass excitation described in the present study. An impulse initiated in one can be conducted to all the recruiting nuclei, which in turn can in all probability effect re-excitation of the site of original discharge, this reverberating activity continuing until all the energy is dissipated. While the diffuse thalamic nuclei are probably independently capable of this rhythmic activity, it is also conceivable that they receive reinforcement from cortical circuits or from the association nuclei or both. By whatever mechanism this provoked burst effect occurs, it furnishes in the diffuse thalamic projection system the basis for a sustained effect with the firing of either a sensory or cortical discharge.

It is interesting to note that, while a discrete sensory stimulus frequently provokes a repetitive discharge in the diffuse nuclei, rapid or high frequency stimulation has a totally different effect. In a dozing animal, such high frequency sensory stimulation obliterates all background synchrony in these nuclei, paralleling a ubiquitous cortical desynchronization (34). This generalized electrical arousal is now known to occur largely through the reticular activating or sensory collateral system (20, 25, 34, 35) which includes at its rostral pole the diffuse nuclei. It seems reasonable from this that these nuclei play a part, through their projections, in the mediation of this effect. Although undoubtedly the case, it has also been shown (35) that the role of these nuclei in cortical arousal, while perhaps important, is not critical.

In general, the diffuse thalamic projection system appears to be organized primarily for associative and integrative function. Through intricate intrathalamic connections, activity can be initiated in large areas of the thalamus with an afferent discharge or by direct stimulation of the diffuse nuclei. While a portion of this effect is ultimately relayed to the cortex, it seems likely that part of the activity is limited to independent thalamic function. That this might be the case is indicated by several considerations. The recruiting nuclei of origin enjoy a peculiarly autonomous position amongst thalamic structures, having in general the common feature of not depending on neocortical connections for existence, since they do not degenerate with neocortical ablation. The complexity of intrathalamic mechanisms further suggests something more than a relay function—the sustained discharge after excitation, multisynaptic conduction which is indicated by wave production even at an intranuclear level, and multiple interconnections all be-

ing features commonly connoting a higher order of neural function. Finally, recruiting waves recorded at the various way stations along their corticopetal route frequently undergo a damping as they ascend. This is particularly clear in the case of the lateralis complex and the pulvinar for, although robust recruiting potentials were invariably recorded from these nuclei, the parietal association cortex to which they project exhibited feeble and often unreliable responses.

It has long been thought on clinical grounds that crude consciousness or perception could exist at a thalamic level, this subcortical primitive appreciation being modified and refined by cortical function. If this is true, it is conceivable that the thalamic portion of the diffuse projection system could represent such a lower brain association region. It is further conceivable that this subcortical integrating center, with its complex structure and all-inclusive sensory inflow, interrelates many of the basic and non-volitional adjustments to environmental stimuli. For through relationship with the hypothalamus it stands in position to alter autonomic and endocrine function, and by descending inhibitory (14, 21) and facilitatory (2, 28, 29) pathways, which either start in or pass through this region, it could effect changes in motor response.

In turn, after modification in this thalamic integrating center, the various sensory impressions are brought to the cortex, the great preponderance of effect, as emphasized in the present study, passing to the frontal association areas. Discrimination of or arousal to a sensory stimulus is probably not dependent on the diffuse thalamic projection system. However, if as suggested it carries subcortically synthesized impressions of an affective nature, it is feasible that, through its projections, changes can be caused in the cortical interpretation and type of response to environmental stimuli. The many clinical and laboratory findings on frontal lobe function, while subject to varying explanation, are in accord with this concept, for lesions interrupting the frontal recruiting pathways at various levels along their ascent produce certain similar neurological deficits. Thus one of the principal losses with destruction of the medial nucleus (32), isolation of the frontal lobes by lobotomy (7, 23), or extirpation of the frontal cortex (13, 19) is an obtundation of the affect component of sensory perception. Although no clinical sensory defect is detectable and the subject is more distractible than normal, he is relatively inert to the emotional implications of environmental stimuli. The abolition of this affect component is so effective that lobotomy has been a useful treatment for patients with intractable suffering from carcinoma for, though these patients still perceive pain, its unpleasant connotations no longer exist (8, 9, 38).

The degree to which either the development or maintenance of frontal cortical functions depends on the diffuse thalamic projection system can only be speculated upon at the present time. It is conceivable that by more complete cortical integration and synthesis these ascending impressions contribute to the frontal lobe functions of complex emotional behavior, higher creative activities and well organized autonomic adjustments.

SUMMARY

The diffuse thalamic projection system has been studied in the monkey by evoking recruiting responses with thalamic stimulation and determining their cortical and subcortical distribution with recording techniques.

The thalamic origins of this system include the centre median, intralaminar, inferior part of the medial, ventralis anterior and anterior reticular nuclei. These components form a functional unit, excitation of any part of which sets the whole into activity. By intrathalamic connections, the recruiting responses from these nuclear origins are conducted to the association nuclei of the thalamus—medial, anterior, lateralis complex and pulvinar. These association nuclei form the final relay for many if not all of the corticopetal recruiting effects. Accordingly, the cortical distribution of responses is limited to associational areas to which these nuclei project. Although organized for mass action on the association cortex, the most significant finding in the more highly developed monkey brain is the high degree of frontal specialization of this system, the great preponderance of effect passing to the frontal association cortex. This suggests that the diffuse thalamic projection system may have a most important role in frontal lobe functions.

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