Projections of the Amygdala to the Thalamus in the Cynomolgus Monkey

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ABSTRACT

The projections of the amygdala to the thalamus in cynomolgus monkeys (Macaca fascicularis) were studied with both anterograde and retrograde axonal tracing techniques. Horseradish peroxidase (HRP) was injected into medial and midline thalamic sites in five animals, and tritiated amino acids were injected into selected amygdaloid regions in a total of 13 hemispheres in ten animals. The findings from the two types of tracer experiments demonstrated the origins, course, and terminal pattern of amygdaloid projections to two thalamic nuclei - medialis dorsalis (MD) and reuniens. Almost all of the amygdaloid nuclei contribute projections to MD, though the greatest proportion arise from the basal group and terminate in discrete, interlocking patches within the medial, magnocellular portion of MD. In addition to this major projection, the central and medial amygdaloid nuclei send a lighter projection to the lateral portion of nucleus reuniens. The amygdalothalamic projections took a variety of routes out of the amygdala before the large majority joined the inferior thalamic peduncle and entered the rostral portion of nucleus reuniens. The amygdalothalamic projections took a variety of routes out of the amygdala before the large majority joined the inferior thalamic peduncle and entered the rostral head of the thalamus where they turned caudally toward their targets. A small number of amygdalothalamic fibers may also run in the stria terminalis.

Key words: amygdala, thalamus, monkey

The projections from the amygdala to the thalamus are currently of great interest for several reasons. First, both regions appear to possess important mnemonic functions. Thus, bilateral temporal-lobe damage involving the amygdala and hippocampus and damage to the medial, periventricular regions of the thalamus have both been consistently associated with profound amnestic syndromes (Scoville and Milner, '57; Victor et al., '71; Brierley, '77). Furthermore, there is evidence that the medial thalamic region that has been implicated in diencephalic amnesia, specifically the nucleus medialis dorsalis (Victor et al., '71; McIntee et al., '76; Markowitsch, '82), receives projections from the amygdala and not from the hippocampus. Second, recent research has indicated that both the amygdala and parts of the medial and midline thalamus are rich in opiate receptors (Kuhar et al., '73; Wamsley et al., '82). In fact the anatomical connections in question link two of the regions with the highest concentration of opiate receptors in the primate brain. Last, amygdaloid efferents to the medial thalamus provide a potentially important route by which a limbic structure may indirectly influence large regions of prefrontal cortex (Nauta, '72; Porrino et al., '81), this cortex being the major target of nucleus medialis dorsalis.

Evidence of direct projections from the amygdala to the thalamus in primates was first provided by the studies of Fox ('49) and Nauta ('61). These authors described degeneration in the magnocellular portion of nucleus medialis dorsalis following lesions in the amygdala of the rhesus monkey. Additional degeneration was noted in nucleus reuniens, nucleus centralis inferior, and nucleus paracentralis (Nauta, '61), as well as in the medial pulvinar (Fox, '49). These earlier studies, however, could provide only a limited description of the amygdaloid projection system, and interpretation of the origin of the system was confounded by the possible existence of thalamic projections from the adjacent allocortex, areas which may have been directly damaged or disconnected in the course of the amygdaloid surgery.

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The newer axonal transport methods for both anterograde and retrograde tracing provide a sensitive means by which the precise amygdalothalamic connections may be detailed. We therefore used the retrograde transport of horseradish peroxidase (HRP) to determine the origin of the thalamic connections within the amygdala, while the thalamic projections of the individual amygdaloid nuclei were investigated with autoradiography.

MATERIALS AND METHODS

The subjects were 15 cynomolgus monkeys (Macaca fascicularis) weighing 2.5–7.5 kg at the time of surgery. The animals were tranquillized with ketamine hydrochloride (10 mg/kg), anesthetized with Nembutal (35 mg/kg), and placed in a stereotaxic apparatus.

Five monkeys received injections of horseradish peroxidase into various medial thalamic regions. Under sterile precautions, bone and dural flaps were opened above the third ventricle at either end of the massa intermedia. The injections were determined from the positions of the third ventricle at either end of the massa intermedia. In three animals injections of 40% HRP (Sigma, type VI) were delivered through a 1-μl Hamilton syringe at a rate of 0.01 μl/3 minutes. In two of these animals (A3 and A5) a total of 0.15 μl of HRP was injected into the nucleus medialis dorsalis and the posterior thalamic midline. The third (A2) 0.13 μl of HRP was injected into the anterior thalamic midline. In an additional animal (A26) 0.8 μl of a 4% solution of HRP (Sigma, type VI) conjugated with wheat germ agglutinin was injected into the anterior thalamus. In the final animal in the series (A7), a 10% solution of HRP in TRIS buffer was delivered iontophotically with a glass pipette into nucleus medialis dorsalis.

Two days after the surgery the monkeys with HRP injections were deeply anesthetized with Nembutal and perfused intracardially with buffered 10% formol saline. The brains were cut in 33-μm coronal sections on a freezing microtome and every sixth section was mounted from either phosphate buffer or Perfix and coated with Kodak NTB2 emulsion. The sections were exposed at 4°C for between 2 and 30 weeks, with one series from every animal being exposed for at least 20 weeks. The sections were developed in Kodak D19, fixed, and counterstained with thionine.

RESULTS

Cytoarchitecture

The lack of a standardized nomenclature for the amygdaloid nuclei (Price, '81a) makes it necessary to choose among the schemes proposed by various investigators. The classification adopted in this study (Fig. 1) is based on the cytoarchitectural descriptions of the primate amygdala by Crosby and Humphrey ('41).

Figure 1 illustrates the relative positions of the amygdaloid nuclei. Five "deep" nuclei may be distinguished, namely, the lateral, lateral basal, medial basal, accessory basal, and central nuclei. There is, in addition, a poorly defined "anterior amygdaloid area" which lies below the endopiriform nucleus (Krettek and Price, '78) and between the central and medial nuclei (Fig. 1a,b). The cytoarchitectural characteristics of these "deep" nuclei have been detailed previously (see Crosby and Humphrey, '41; Lauer, '45, Jiminez-Castellanos, '49). Although there is no absolute border between the lateral basal and medial basal nuclei they are treated as distinct, a viewpoint supported by evidence of connectional differences (Hertzog and Van Hoesen, '76; Pandya et al., '81).

Abbreviations

A Anterior amygdaloid area
AC Anterior commissure
ACC B Accessory basal nucleus
AHA Amygdalohippocampal area
AM Nucleus anterior medialis
AV Nucleus anterior ventralis
BNST Bed nucleus of stria terminalis
Ct Tail of caudate
Cde Nucleus centrale densocellularis
CE Central nucleus
CL Claustrum
Cl Nucleus centrale lateralis
Cic Nucleus centrale latocellularis
CoMd Nucleus centrum medianum
CTA Cortical transition area
EC External capsule
END Endopiriform nucleus
F Fornix
GP Globus pallidus
H Hippocampus
IC Internal capsule
ITP Inferior thalamic peduncle
LAT Lateral nucleus
LB Lateral basal nucleus
MB Medial basal nucleus
ME Medial nucleus
MD Nucleus medialis dorsalis
MDmc Nucleus medialis dorsalis
MDpe Nucleus paraventricularis
OC Optic chiasm
OT Optic tract
P Putamen
Pa Nucleus paraventricularis
PAM Periamygdaloid cortex
Pen Nucleus paracentralis
Pf Nucleus parafascicularis
R Nucleus reticularis
Re Nucleus reuniens
SI Substantia innominata
SM Stria medullaris
ST Stria terminalis
TMT Mammillothalamic tract
VA Nucleus ventralis anterior
VAmc Pars magnocellularis
X Area X
Fig. 1. Coronal sections taken at 1-mm intervals through the amygdaloid complex showing the major nuclear divisions (thionine stain).
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The superficial nuclei of the amygdala, which lie on the medial surface of the temporal lobe, comprise the medial and cortical nuclei, the periamygdaloid cortex, and the corticoamygdaloid transition area (Fig. 1). The medial nucleus is composed predominantly of small to medium multipolar neurons which are most densely packed near the medial edge of the nucleus. The cortical nucleus lies ventral to the medial nucleus and medial to the accessory basal nucleus, with which it has no clear border (Fig. 1b,c). Ventral and anterior to the cortical nucleus lies the periamygdaloid cortex, which is distinguished from the cortical nucleus by its greater preponderance of pyramidal cells and a wider, more uniform layer III (Fig. 1). Located between the periamygdaloid cortex and the entorhinal cortex, and medial to the basal medial nucleus, is a region of pyramidal-type cells which show almost no signs of lamination. This is the corticoamygdaloid transition area, which is found along the caudal two-thirds of the amygdala. In addition to these areas, a transitional "amygdalohippocampal area" lying between the amygdala and the hippocampus at the caudal extreme of the amygdala can also be identified (Fig. 1d).

The nomenclature for the thalamus is taken from the description of Olcese et al. (1952). This classification, which is based on the cytoarchitectural appearance of the thalamus of the rhesus monkey (Macaca mulatta), is equally applicable to the cynomolgus monkey. Two thalamic nuclei, medial dorsalis (MD) and reuniens, are considered in this study. Nucleus medialis dorsalis, which occupies much of the posterior medial quadrant of the thalamus, may be divided into four subareas: pars magnocellularis, parvo cellularis, multififormis, and densocellularis. The medial portion of MD, pars magnocellularis (MDmc), is identified by its large, well-spaced spherical neurons. Nucleus reuniens, one of the midline nuclei, extends along the ventral surface of the massa intermedia, lying adjacent and dorsal to the third ventricle. This nucleus is composed of small, heterogeneous neurons.

HRP experiments

Amygdaloid HRP label. Figure 2 illustrates the extent of the thalamic injections in four of the five brains studied. The figure depicts the region around the injection site in which the HRP reaction product is distinguishable under brightfield conditions. Three monkeys (A3, A5, A7) received injections which involved almost the entire extent of the anterior portion of the midline within the amygdala. These injections always involved, in addition, the adjacent nuclei paraventricularis, centralis superior, centralis inferior, centralis intermedialis, centralis densocellularis, and the medial aspect of the parvocellular portion of medialis dorsalis (Fig. 3). In one case (A3) the injection site was centered in the caudal midline thalamic nuclei and extended into the medial aspect of nucleus parafascicularis, the most caudal portion of nucleus reuniens, the medial habenula, and much of nucleus medialis dorsalis, while in the other two cases (A5, A7) some HRP leaked into the transected corpus callosum.

These three experiments, which produced very similar patterns of amygdaloid label, provided evidence of a moderate amygdalothalamic projection system. The findings in monkey A5, which were typical, are illustrated in Figure 4. Cells labelled with HRP were found throughout the amygdala, but the greatest concentration always occurred in the medial basal nucleus. This nucleus contained approximately one-half of the total HRP-positive cells in the amygdala of animals A3, A5, and A7. Labelled cells were found throughout the medial basal nucleus (Fig. 4), though there was a tendency for them to be concentrated in its medial half. The lateral basal nucleus contained the second highest number of HRP-positive cells in these three monkeys, though there were considerably fewer than in the medial basal nucleus. A small number of labelled cells was found in the accessory basal nucleus, the periamygdaloid cortex, and the corticoamygdaloid transition area. Only occasional labelled cells were seen in the remaining amygdaloid nuclei. There was no evidence that the HRP-positive cells were concentrated in any particular cytoarchitectural subdivision within the amygdaloid nuclei.

HRP was injected into the anterior thalamic midline in two animals (A2, A26). In both cases, the HRP spread throughout nuclei anterior medialis, centralis densocellularis, centralis lateralis cellularis, alaris, rotundus, and the rostral half of nucleus paraventricularis but not into nuclei medialis dorsalis (Fig. 2).

In animal A26 the injection extended ventrally to include all of the anterior portion of nucleus reuniens and the most dorsal portion of the dorsomedial hypothalamic nucleus. Numerous cells labelled with HRP were found throughout the dorsal amygdala in this case. The greatest concentrations of these labelled cells occurred in the medial nucleus and in the medial portion of the central nucleus. The remaining amygdaloid nuclei contained only a handful of labelled cells, with an occasional cell being present in each amygdaloid nucleus (Fig. 4). A similar anterior thalamic injection was placed in animal A2, though the injection extended ventrally only to the dorsal margin of nucleus reuniens. In this case, there was only a very small accumulation of labelled cells in the central and medial nuclei and in the amygdalohippocampal area, and a total of only one or two cells each were found in most of the other amygdaloid nuclei.

Cells labelled with HRP were also found in a variety of sites adjacent to the amygdala (Fig. 4). The piriform, entorhinal, prorhinal, and perirhinal cortices (Van Hoesen and Pandya, 1975) all contained significant numbers of labelled cells following the injections centered in MD (A3, A5, A7). These cortical cells, which were mainly pyramidal, were located in layers III and V. The substantia innominata contained retrogradely labelled cells in all animals. This label was particularly dense in animal A26, in which the anterior thalamic projection was particularly well labelled.

Well-defined anterograde HRP label was observed only in the amygdala of animal A26 (Fig. 2). The anterograde label in this case was present throughout much of the complex, with the greatest concentration appearing in the lateral basal and medial nuclei and in the medial portion of the central nucleus. In contrast, the lateral and accessory basal nuclei and the lateral portion of the central nucleus contained little anterograde label.

Course of amygdalothalamic connections. Labelled fibers running between the amygdala and the thalamus were observed in several animals (A5, A5, A26). Although it was impossible to determine whether these fibers contained anterograde or retrograde label, the relative scarcity of anterograde label within the amygdala makes it likely that the direction of the majority of the fibers is amygdalothalamic. The fibers typically took one of two routes through the amygdala. One group of fibers could be seen either cutting across the face of the rostral amygdala or running in the external capsule adjacent to the lateral
nucleus. Some of these fibers could be followed into the white matter between the rhinal sulcus and the amygdala and into the ventral amygdala. These sets of axons merged in the substantia innominata with the other major group of labelled axons, which ran directly through the dorsal amygdala.

The presence of a small number of HRP-positive fibers in the stria terminalis in two animals (A5, A26) suggests that at least a small component of the amygdalothalamic connections may travel in this fiber tract. In addition, labelled fibers were seen running in the external capsule between the claustrum and the putamen in case A5. These fibers could be followed ventrally into the region of the anterior perforated substance, just dorsal to the rostral amygdala.

**Autoradiographic experiments**

**Thalamic amino acid label.** The amygdala was injected with tritiated amino acids in a total of 13 hemispheres. Figure 5 depicts the locus and extent of the injection sites. The size of each injection was defined as the region in which an appreciable accumulation of silver grains could be observed within the perikaryon after a development period of at least 6 weeks. Each of the amygdaloid nuclei, with the exception of the anterior area, was involved in at least one case. There was extraamygdaloid spread in only three injections: into the head of the hippocampus in one (A13), into the entorhinal cortex in another (A10), and into both of these regions in the third (A4).

Terminal label was found in the magnocellular part of MD (Fig. 6) in those cases in which the injection was centered in either the medial basal nucleus (A4, A10, A13), or the lateral basal nucleus (A6, A21-left, A21-right), or the accessory basal nucleus (A18, A20-left, A20-right), or the ventral portion of the lateral nucleus (A16). In contrast, injections involving the dorsal portion of the lateral nucleus (A22-right), the central nucleus (A17), or the medial nucleus (A22-left) did not result in label within MD.

The thalamic label in MDmc always occurred in patches which were often interlinked, thereby forming a complex reticular pattern. There was little overlap between the tha-
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Fig. 3. Brightfield photomicrograph of injection site in animal A5 (thionine stain).

lamic terminal fields of the different cases, indicating that the projections from the various amygdaloid nuclei terminate in distinct subareas of MDmc (Fig. 7). In all cases the projection to MDmc was concentrated within the rostral two-thirds of the nucleus. Given the apparent topography of the projections, however, the absence of label in caudal MDmc could reflect a failure to inject the appropriate locus in the amygdala. Injections centered in the lateral and accessory basal nucleus produced the lightest terminal label observed in MDmc (A16, A18, A20-left, A20-right). An amygdaloid projection to the contralateral MDmc was observed, but only in the animals with the largest amygdaloid injections (A4, A6). This projection always fell within the same loci as the ipsilateral one but was considerably lighter and smaller.

Light terminal label was found in the ipsilateral portion of nucleus reuniens (Fig. 7) in animals A17 and A22-left following injections involving primarily the central and medial nuclei, respectively. This label, which was particularly light in the animal with an injection in the medial nucleus (A22-left), was restricted to the rostral half of nucleus reuniens just ventral to nucleus centralis latocellularis. The projection was confined to the lateral portion of nucleus reuniens, an area distinguished from the medial portion by its rounder, more deeply staining cells. No label was found in MD in either of these cases.

There was no evidence of a projection to any other thalamic nucleus in those cases in which the injection was restricted to the amygdala. Although terminal label was observed in the midline and anterior thalamic nuclei in A4 and A13, there was spread of the isotope into the rostral head of the hippocampus in both cases, and the pattern of thalamic label matched that seen after injections entirely confined to the hippocampus (Rosene and Van Hoesen, '77; Aggleton and Mishkin, '82).

Course of amygdaloid efferents. The route of the amygdaloid projections to the thalamus could be traced back through the inferior thalamic peduncle to the ventral amygdalofugal pathway. Fibers leaving the amygdala took either a direct dorsal or an indirect ventral route (Fig. 8, section 1) before joining the ventral amygdalofugal pathway. These latter fibers left the amygdala ventrally to join the white matter between the medial basal nucleus and the rhinal sulcus. The efferents then passed either anteriorly around the rostral face of the amygdala or laterally and then dorsally to run in the most medial edge of the external capsule, adjacent to the lateral nucleus. The different sets of ventrally exiting fibers appeared to converge above the dorsal amygdala with the majority of efferents that passed directly out of the dorsal amygdala, where they combined to form the ventral amygdalofugal pathway (Fig. 8, sections 1, 2). The proportion of fibers leaving the amygdala by the ventral route appeared greatest in those cases in which the injection was centered in the medial basal or lateral basal nuclei.

Label in the ventral amygdalofugal pathway could be seen passing below the anterior commissure through the substantia innominata and the most ventral portion of globus pallidus before rising medial to the anterior limb of the internal capsule to reach the bed nucleus of the stria terminalis (Fig. 8, sections 2 and 3). Some of the fibers in the more caudal portions of the ventral amygdalofugal pathway were seen to join the inferior thalamic peduncle and ascend above the posterior hypothalamus to enter the rostral pole of the thalamus. These amygdaloid efferents formed diffuse bundles which entered the head of the thalamus and passed medial to nucleus reticularis before running caudally through the medial, magnocellular portion of ventralis anterior (Fig. 8, section 4). These fiber bundles entered nucleus paracentralis and then crossed nucleus paracentralis and entered the head of mediialis dorsalis where they fanned caudally and dorsally to terminate within the magnocellular portion of the nucleus (Fig. 8, sections 5 and 6).

In all cases, with the exception of A22-right, transported label was also carried in the stria terminalis. Although labelled fibers were not observed to branch off the stria and join the thalamus directly, it is possible that some amygdalothalamic fibers run the length of the stria to its bed nucleus before turning caudally to enter the thalamus. Unfortunately, the close proximity of the stria terminalis fibers entering the bed nucleus with those in the inferior thalamic peduncle (Fig. 8, sections 2, 3) made it impossible to determine whether or not the stria terminalis does contribute directly to the amygdalothalamic projection. Finally, other amygdaloid efferents could be seen entering the external capsule and rising dorsal and medial to the claustrum (Fig. 8, all sections). It was not possible to determine, however, whether any of these fibers terminated in the thalamus.

DISCUSSION

The present study has confirmed the existence of amygdaloid efferents originating in the basolateral group of amygdaloid nuclei that terminate in nucleus medialis dor-
Organization of amygdalothalamic projections

Injections of HRP centered in nucleus medialis dorsalis revealed amygdaloid projections arising predominantly from the basal group of nuclei. The medial basal nucleus provided the majority of this input, with the lateral and accessory basal nuclei supplying a smaller but significant contribution. The autoradiographic experiments demonstrated that these amygdaloid efferents project to the magnocellular portion of nucleus medialis dorsalis (MDmc), with the various amygdaloid subdivisions terminating in different portions of the nucleus. Thus, the lateral amygdala was found to project to anteroventral MDmc, the lateral basal region to the central core of MDmc, and the accessory and medial basal nuclei to the more dorsal portions of MDmc. A light projection to the contralateral MDmc was also observed in the animals with the largest amygdaloid injections. Finally, the concordance between the HRP and autoradiographic experiments indicates that little if any HRP was transported to the amygdala by fibers of extrathalamic origin running through the injection site. On the other hand, it is possible that some of the retrograde amygdaloid label found after HRP injections into the anterior thalamic midline originated from amygdaloid fibers projecting through the injection site to MDmc. However, the markedly different pattern of amygdaloid HRP label that resulted from injections in the anterior as compared with the posterior medial...
Fig. 5. Distribution of amino acid injections throughout the rostrocaudal extent of the amygdala. White numerals refer to separate cases, and l and r refer to left and right hemispheres, respectively. Case A20-right is not shown as it largely overlaps with A20-left.
thalamus (Fig. 4) indicates that any such uptake by fibers of passage can account only for a small proportion of the retrograde label.

It is unclear whether the amygdala projects throughout MDmc. Discrete injections of amino acids within the amygdala produced small patches of termination, as first mentioned by Price and Amaral ('81). These patches were found to interlock with one another and thereby fill much of the rostral portion of MDmc. Furthermore, these patches were less apparent in the largest injections, suggesting that the spaces between the patches had been filled in. As the present series of injections did not totally cover the amygdala, it is possible that the entire extent of MDmc receives amygdaloid projections. On the other hand, the absence of terminations in caudal MDmc in every one of the cases suggests that this region may well not receive amygdaloid efferents.

A light projection to the rostral portions of nucleus reuniens was observed following injections of tritiated amino acid that involved the central and medial nuclei. In line with this, HRP was placed in the rostral thalamic midline in two animals, but only the injection that involved nucleus reuniens produced appreciable retrograde label in the amygdala; this label was concentrated in the medial and central nuclei. Thus, both the anterograde and retrograde transport experiments demonstrate a direct projection from the central and medial nuclei to the rostral portion of nucleus reuniens. Unlike the amygdaloid projections to MDmc, those to nucleus reuniens appeared to be ipsilateral only.

The amygdalothalamic projections followed two routes out of the amygdaloid nucleus. Some amygdaloid efferents coursed ventrally to pass around the anterior and lateral borders of the amygdala, while others passed out of the dorsal amygdala directly. These two sets of efferents combined to form the ventral amygdalofugal pathway, part of which sweeps medially and caudally through the substantia innominata and then rises dorsally to pass behind the anterior commissure into the bed nucleus of the stria terminalis. A caudal component of this pathway joins the inferior thalamic peduncle and rises into the rostral tip of the thalamus. These latter fibers then run caudally through the magnocellular portion of nucleus ventralis anterior and nucleus paracentralis before entering the rostral pole of MD. In addition, there was evidence that the stria terminalis, and possibly the external capsule as well, carry amygdalothalamic projections, though it was never possible to follow labelled fibers through the entire length of these tracts and so confirm these alternative routes. Last, no evidence could be found of a thalamic projection in the stria medullaris, though such a route may exist in the rat (Heimer, '72).

Several minor discrepancies were noted between the present results and those of previous studies of amygdalothalamic projections in the primate. For example, no conclusive evidence could be found from either the anterograde or retrograde transport experiments of amygdaloid projections to any of the thalamic midline nuclei other than nucleus reuniens, though such projections have been reported following an injection of tritiated amino acids.
into the caudal portion of the central nucleus (Price and Amaral, '81). These additional projections would appear to be very light, however, as there was no evidence of an accumulation of HRP-positive cells in the central nucleus in cases A2 and A3, in which the injections were located in the anterior and posterior midline thalamic nuclei, respectively. Also, a much larger number of amygdalothalamic projections than described here was suggested by Porrino et al. ('81), though it is evident that in the latter study this was due, at least in part, to the spread of amino acids into the adjacent temporal cortex and hippocampus. Finally, no evidence could be found of a projection to the medial pulvinar (Fox, '49; Price and Amaral, '81).

The only other species in which amygdalothalamic projections have been studied systematically is the rat, and the overall pattern of the projections in this species appears to match closely those in the monkey. As in the monkey, nucleus medialis dorsalis in the rat is the major thalamic target of the amygdaloid complex (Krettek and Price, '77). This projection arises from the basolateral nucleus and the endopiriform nucleus and terminates, respectively, in the medial and central portions of MD. There is also some evidence that the projections from the basolateral nucleus have a crude topography, but, unlike the case in the monkey, these projections in the rat have a rostrocaudal organization and do not appear to terminate in distinctive patches. Finally, there is a report of a light amygdaloid projection to nucleus reuniens which arises predominantly from the medial nucleus and the anterior area (Herkenham, '78). However, the failure to find evidence of similar thalamic afferents in the cat (Krettek and Price, '77) indicates that interspecies variability in amygdalothalamic projections may be much greater than that found thus far between rat and monkey.

**Relationship of amygdalothalamic projections to other amygdaloid connections**

While the majority of amygdaloid projections to the forebrain are reciprocated (Aggleton et al., '80; Price, '81b), the amygdalothalamic connections provide a clear exception. Most amygdaloid efferents to the thalamus terminate in MDmc, yet it has been shown repeatedly that thalamic projections to the amygdala arise not from MDmc but from some of the midline nuclei, from some of the intra-
Fig. 8. Coronal sections illustrating the pattern of labelled fibers, shown in dashes, emerging from a representative amygdaloid injection of amino acid (animal A6). Successive sections are approximately 2 mm apart. This figure depicts the major efferent routes from the amygdala into the ventral amygdalofugal pathway, the stria terminalis, and the external capsule. The locus of fibers in the stria terminalis is indicated by dense dashes, both ventrally and dorsally, in sections 3-6. The termination of the thalamic projection in MDmc is shown dotted.

laminar nuclei including nucleus parafascicularis and nucleus subparafascicularis, and from the medial pulvinar (Aggleton et al., '80; Mehler, '80). Only nucleus reuniens appears to possess reciprocal amygdaloïd connections, the lateral portion of this nucleus both receiving amygdaloïd efferents and projecting back to the amygdala (Mehler, '80; Aggleton, unpublished results). It is interesting to note, however, that most of the thalamic nuclei that do project to the amygdala (i.e., the midline and intralaminar nuclei) contain high concentrations of opiate receptors, as does the amygdala itself (Wamsley et al., '82). This concordance may reflect the existence of "opiatergic tracts" that course both ways between the amygdala and the thalamus. Recent evidence on the distribution of enkephalin-containing cell bodies within the amygdala of the rat indicates that the central nucleus is the major source of opiate efferents (Roberts et al., '82). This evidence combined with indications that the levels of opiate receptors in MD are
lower than in the adjacent midline and intralaminar nuclei (Wamsley et al., '82) suggests that the projection from the amygdala to the medial nuclei of the thalamus is not part of the putative opiateergic system.

Nauta ('82, '72) has already noted that the existence of amygdalothalamic projections provides an indirect route by which the amygdala may influence prefrontal cortex. The medial, magnocellular portions of MD which receive amygdaloid afferents project to the thalamus in the orbitofrontal, medial prefrontal, and anterior cingulate cortices (Porrino et al., '81; Price, '81b). These direct amygdaloprefrontal projections arise from the basal group of nuclei, the same nuclei that provide the majority of the efferents to the prefrontal cortex. Thus, the same amygdaloid region may project both directly and indirectly through MDmc to the orbital and medial prefrontal regions. Furthermore, the organized pattern of the amygdalothalamic projections suggests that the different amygdaloid nuclei may be indirectly linked with different regions of prefrontal cortex. Neither the direct nor indirect amygdaloprefrontal projections have yet been detailed, however, and so it is unclear whether or not these two projection systems are congruent.

Amygdalothalamic projections and memory

An indicated earlier, chronic anterograde amnesia in man is associated with damage in two regions—the medial temporal lobe and the medial diencephalon. The existence of projections from the hippocampus and amygdala to the medial diencephalon through the fornix and inferior thalamic peduncle, respectively, indicates that the medial temporal and medial thalamic regions may constitute an interconnected system subserving memory. Indirect evidence of the importance of the inferior thalamic peduncle for memory processes is provided by the frequent failure of fornix lesions alone to produce a notable degree of amnesia in man, a finding which suggests that the remaining medial temporal-diencephalic pathway can support mnemonic functions. Furthermore, nucleus medialis dorsalis, to which the amygdala but not the hippocampus projects, is the thalamic structure most frequently implicated in diencephalic amnesia (Victor et al., '71; Markowitsch, '82).

The notion that amygdalothalamic projections are part of a temporodiencephalic memory system is also supported by neuropsychological studies in monkeys. Thus, combined ablation of the amygdala and the hippocampus results in a far more severe memory loss than does ablation of either structure alone (Mishkin, '78). Similarly, combined disconnection of these two structures from the diencephalon yields a much more severe memory loss than does disconnection of either structure alone (Bachevalier et al., '82). Finally, combined destruction of the major thalamic targets of the amygdala and the hippocampus, namely, MDmc and the anterior nuclei, yields a more severe amnesia than does destruction of either target alone (Aggleton and Mishkin, '83a,b). In short, there is now both clinical and experimental evidence that both the amygdalothalamic projections and the hippocampodiencephalic projections are part of an integrated system for memory (Mishkin, '82). By confirming that MDmc is the main thalamic target of the amygdala, the present experiments strengthen the conclusion that this nucleus has an important mnemonic role. This, in turn, suggests the intriguing but still untested possibility that the areas to which MDmc projects, namely, the medial and orbital prefrontal cortex, may likewise play an important role in memory.

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LITERATURE CITED


