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The connexions of the amygdala

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The amygdaloid nuclei have been the subject of considerable interest in recent years and have been studied with a variety of experimental techniques (cf. Gloor, 1960). From the anatomical point of view attention has been paid mainly to the efferent connexions of these nuclei (Adey and Meyer, 1952; Lammers and Lohman, 1957; Hall, 1960; Nauta, 1961), and it is now generally accepted that there are two main efferent pathways from the amygdala, the well-known stria terminalis and a more diffuse ventral pathway, a component of the longitudinal association bundle of the amygdala. It has not generally been recognized, however, that in studying the efferent connexions of the amygdala it is essential first to exclude a contribution to these pathways from the pyriform cortex, especially in view of the opinion of Cajal (1911) that the stria terminalis arises in this cortical area and represents an 'olfactory projection pathway'. Although recent experimental work has established that the pyriform cortex does not, in fact, contribute fibres to the stria terminalis it is now clear that the major efferent projection from the pyriform cortex passes through the amygdala and has a distribution identical with that of the longitudinal association bundle and the ventral amygdalo-fugal pathway (Powell, Cowan, and Raisman, 1963). For this reason it is not possible, with large lesions of the amygdala, to distinguish between the interruption of fibres which are merely passing through the region and those which may be arising in the amygdaloid nuclei. Thus the question arises whether the ventral pathway may rightly be considered an amygdalo-fugal system as well as a pyriform cortex projection pathway, and at present this remains undecided. The afferent connexions of the amygdala (with the exception of those derived from the olfactory bulb) have, in general, received less attention than the efferents, although there are several reports of caudally directed fibres in the stria terminalis and of afferent fibres to the amygdala in the ventral pathway (Nauta, 1958, 1962; Sanders-Woudstra, 1961; Shute and Lewis, 1961; Hilton and Zbrożyna, 1963; Valverde, 1963). As yet there has been no study in which an attempt has been made to integrate these connexions and the other known amygdaloid afferents or to relate this information to what is known of the efferent connexions of the amygdala.

MATERIAL AND METHODS

The brains of 26 rats in which a variety of stereotactic or surgical lesions had been placed in the diencephalon and basal forebrain areas were used in this study. Following survival periods of five to seven days the animals were perfused with 10% formol-saline and after further fixation the brains were either embedded in paraffin wax or sectioned on a freezing microtome. All the brains were cut in the coronal plane, and from each a regularly spaced series was stained, the paraffin sections according to the original Nauta and Gygax (1951) technique and the frozen sections with the conventional Nauta (1957) method. For the exact delimitation of the lesions and of the areas showing degeneration, closely spaced series of sections from all the brains were also stained with thionin.

NORMAL MORPHOLOGY

In the rat the amygdala occupies a large part of the ventral aspect of the cerebral hemisphere extending from the level of the diagonal band nucleus back almost to the caudal pole. As previous descriptions of this region have been given by Gurdjian (1928) and Brodal (1947), and as the classification adopted in the present investigation follows to a large extent that of the latter author, only a brief account of the amygdaloid nuclei will be given here.

In Fig. 1 three coronal sections through the amygdala have been outlined at representative rostro-caudal levels. Seven principal nuclei can be distinguished. At the most rostral level the anterior amygdaloid area and the nucleus of the lateral olfactory tract can be seen; the former represents the junctional zone between the olfactory tubercle in front and the definitive amygdaloid nuclei behind, while the latter is a small mass of cells capping the caudal end of the lateral olfactory tract. The next section is at approximately the middle of the antero-posterior extent of the amygdala and shows the relationship of several of the main nuclei. Dorso-medially is the small-celled central nucleus which is closely related rostrally to the bed nucleus of the stria terminalis; ventro-medial to it is the medial

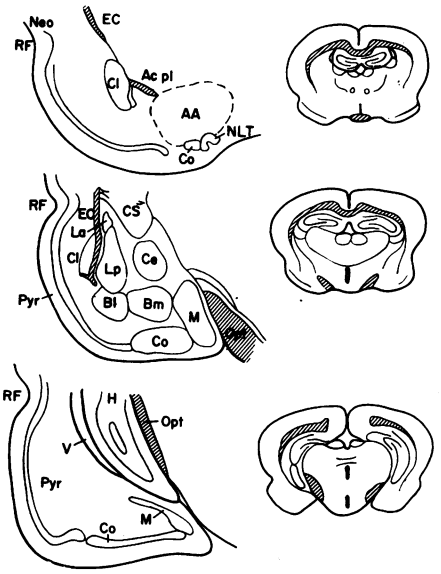


FIG. 1. *The position of the principal amygdaloid nuclei in coronal sections at three rostro-caudal levels.*

Neo	*neocortex*
EC	*external capsule*
RF	*rhinal fissure*
Cl	*claustrum*
Acpl	*posterior limb of anterior commissure*
AA	*anterior amygdaloid area*
NLT	*nucleus of the lateral olfactory tract*
Co	*cortical nucleus of amygdala*
CS	*striatum*
La	*anterior part of lateral nucleus of amygdala*
Lp	*posterior part of lateral nucleus of amygdala*
Ce	*central nucleus of amygdala*
Pyr	*pyriform cortex*
Bl	*lateral part of basal nucleus of amygdala*
Bm	*medial part of basal nucleus of amygdala*
M	*medial nucleus of amygdala*
Opt	*optic tract*
H	*hippocampus*
V	*ventricle*

nucleus, and directly ventral to it are the two parts of the basal nucleus, the large-celled baso-lateral and the small-celled baso-medial. The lateral amygdaloid nucleus consists of a larger posterior part containing large, deeply staining cells and a much smaller and less well-defined anterior part lying in the angle between the external capsule laterally and the central nucleus medially. On the posterior section only the cortical and medial nuclei are seen; the cortical nucleus is very similar in structure to, and is poorly demarcated from, the pyriform cortex laterally; it extends over the entire antero-posterior extent of the amygdala.

RESULTS

The results of the experimental material may be presented conveniently in two sections dealing with the afferent and efferent connexions of the amygdala respectively. Afferent fibres to the amygdala have been described as coming from four principal sites: the diencephalon, the olfactory bulb, the olfactory tubercle, and the pyriform cortex; as the detailed evidence relating to both the direct and indirect olfactory connexions has been given elsewhere (Powell, Cowan, and Raisman, 1965), only the experiments bearing upon the afferents from the diencephalon will be described in this paper. Thereafter, an account will be given of experiments with lesions of varying size in the amygdala to show first the total efferent projection of this region, and then the differential origin of the two main efferent pathways.

Of several experiments with lesions in the hypothalamus and preoptic areas only one will be described in detail. In experiment P.16 the lesion lies mainly in the lateral preoptic area and has probably interrupted all the fibres passing from the diencephalon to the amygdala. The area of destruction extends from the level of crossing of the anterior commissure rostrally to just behind the optic chiasma. The lateral preoptic and lateral hypothalamic areas are extensively damaged but dorsally the internal capsule and the zona incerta have not been involved, and the medial hypothalamic nuclei are similarly spared (Fig. 2). From this lesion degenerating fibres can be traced into the amygdala via two pathways: dorsally, by way of the stria terminalis and ventrally, through the anterior amygdaloid area. At the level where the stria terminalis enters the medial preoptic area behind the anterior commissure, numerous degenerating fibres can be seen clearly, passing dorsally into the stria. Although here they spread out over the whole mediolateral extent of the bundle, there is a heavier concentration of degenerating fragments in its medial third. At more caudal levels, where the stria is sectioned transversely just below the fimbria, there is again some degeneration throughout its cross-sectional area, but along the ventral aspect of the stria the degeneration is appreciably heavier (Fig. 3). The degenerating fibres retain this distribution back to the level of the caudal third of the amygdala where the stria is again vertically disposed, and they become segregated into its medial part. Upon entering the amygdala, the degenerating fibres course laterally around the ventral border of the central amygdaloid nucleus (Fig. 4), but the further distribution of this degeneration cannot be distinguished from that in the ventral pathway. This

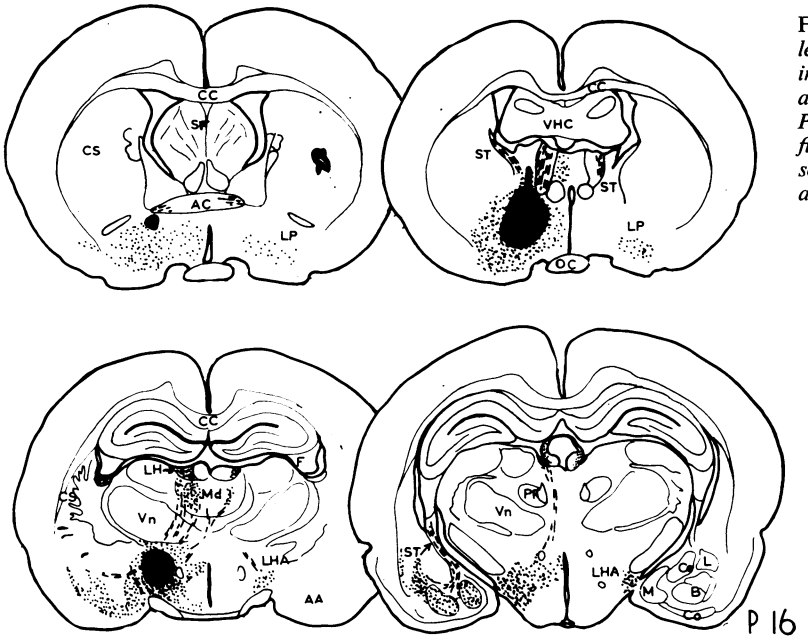
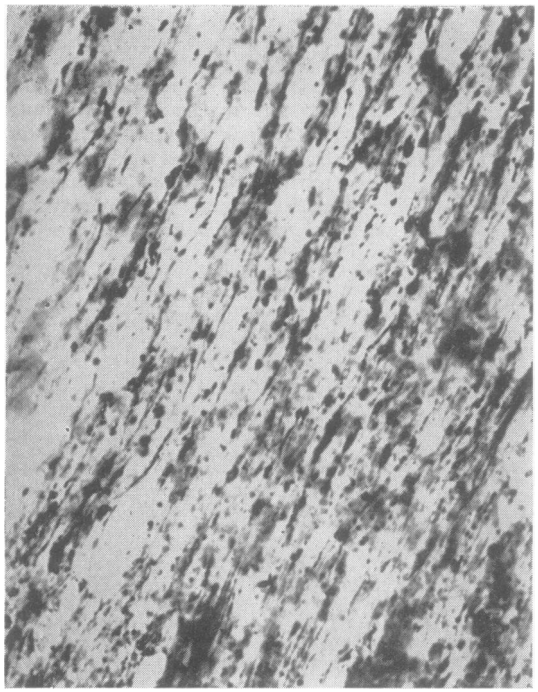


FIG. 2. *Diagram to show the lesion and distribution of the resulting degeneration in the amygdala and diencephalon in experiment P16. In this and the subsequent figures the lesion is shown in solid black and the degeneration as interrupted lines and dots.*

CC	*corpus callosum*
CS	*striatum*
SF	*septo-fimbrial nucleus*
AC	*anterior commissure*
LP	*lateral preoptic area*
ST	*stria terminalis*
VHC	*ventral hippocampal commissure*
OC	*optic chiasma*
LH	*lateral habenular nucleus*
Md	*medio-dorsal nucleus of thalamus*
Vn	*ventral nucleus of thalamus*
LHA	*lateral hypothalamic area*
AA	*anterior amygdaloid area*
F	*fimbria*
PF	*parafascicular nucleus of thalamus*
M	*medial nucleus of amygdala*
Ce	*central nucleus of amygdala*
L	*lateral nucleus of amygdala*
B	*basal nucleus of amygdala*
Co	*cortical nucleus of amygdala*

ventral pathway extends from the lateral aspect of the lesion directly into the anterior amygdaloid region (Fig. 2), and, judging from the density of the degeneration in the anterior amygdaloid area, it is clearly a major source of afferents to the amygdaloid nuclei (Fig. 5). Behind the anterior amygdaloid area, this degeneration becomes intermingled with that from the stria terminalis. The central amygdaloid nucleus shows little or no sign of preterminal degeneration, but in its ventral third there is a marked fragmentation of fibres of passage, which are passing laterally into the lateral amygdaloid nucleus. The posterior, large-celled part of the lateral nucleus shows heavy degeneration in a typical pericellular arrangement, but the small-celled, anterior part of this nucleus is quite free of degeneration. Although both parts of the basal nucleus show unequivocal evidence of preterminal degeneration (Fig. 6), the medial part of this nucleus is clearly demarcated from the large-celled lateral amygdaloid nucleus by the sudden transition in the density of the degeneration, that in the baso-medial being decidedly sparser. In the medial amygdaloid nucleus, there is again a good deal of degeneration, about equivalent in density to that seen in the lateral nucleus. The cortical amygdaloid nucleus contains very little degeneration, except along its dorsal aspect where there is considerable fibre fragmentation. A few fibres can also be traced into the white matter deep to the pyriform cortex and beneath the claustrum, but these structures themselves are quite free of degeneration. In addition to these two pathways to the amygdala, degeneration can be seen passing from the lesion to several sites in both the diencephalon and telencephalon, and in particular to the mediodorsal nucleus of the thalamus, into the stria habenularis, and into the more rostral and caudal parts of the medial forebrain bundle. As it is not relevant to the present study, however, the course and distribution of these degenerating fibres will not be considered further except to mention that some of the degenerating fibres which enter the stria habenularis can be seen to cross in the habenular commissure to the stria of the opposite side, in



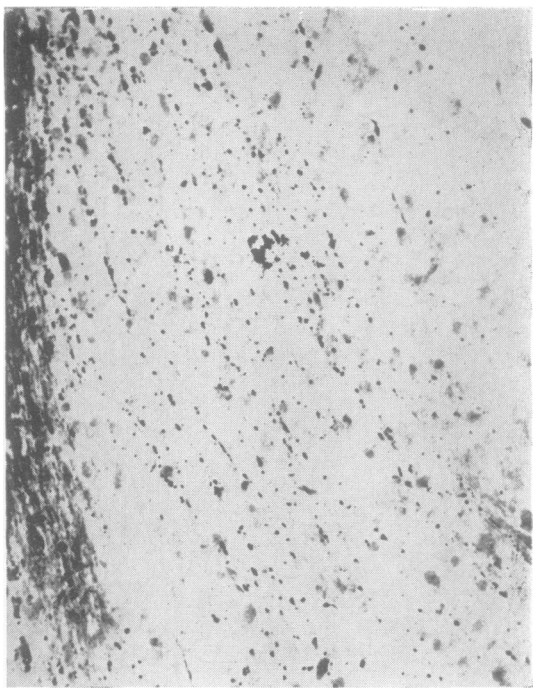
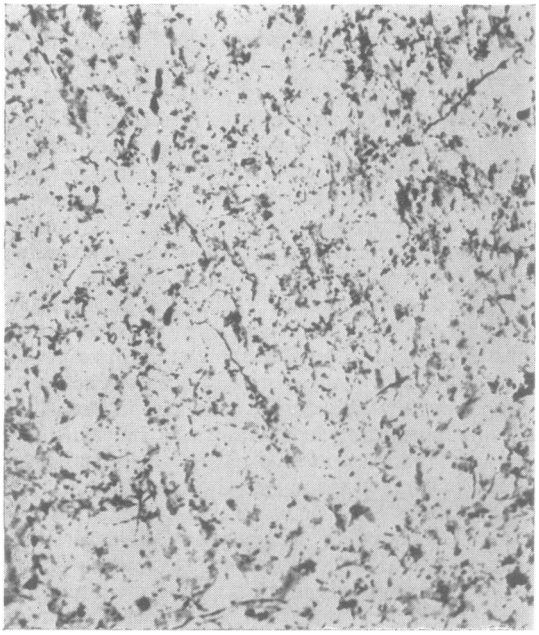


FIG. 3. *Photomicrograph to show degeneration of caudally directed fibres in the ventral part of the stria terminalis in experiment P16. Nauta method.* × *90.*

FIG. 4. *Photomicrograph of degenerating amygdala-petal fibres passing from the stria terminalis (on the left) around the ventral border of the central nucleus of the amygdala to enter the lateral and basal nuclei. Experiment P16. Nauta method.* × *480.*



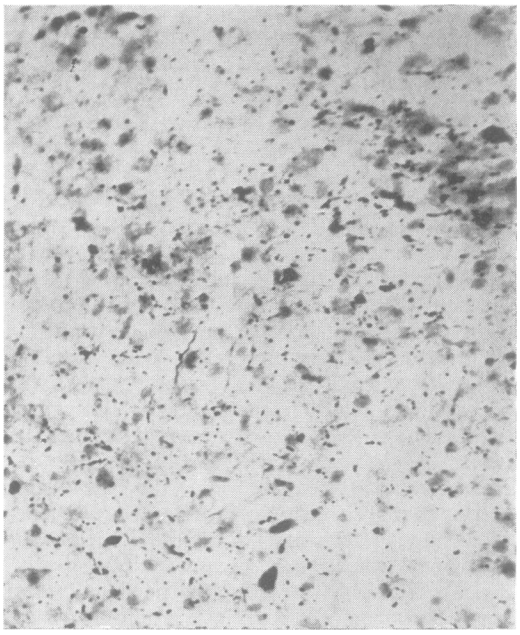


FIG. 5. *Photomicrograph to show fibre degeneration in the ventral pathway to the amygdala after a lesion in the lateral preoptic area. Nauta method.* × *480.*

FIG. 6. *Photomicrograph to show heavy terminal degeneration in the baso-lateral amygdaloid nucleus in experiment P16. Nauta method.* × *480.*

which they pass forwards and downwards to the lateral preoptic and lateral hypothalamic areas, through which they run caudally in the medial forebrain bundle as far as the premamillary region.

As the lesion in brain P16 is fairly large, and is situated rather close to the anterior amygdaloid area, a second experiment, P5, with an appreciably smaller and more caudally placed lesion will also be described. In this experiment, a small electrolytic lesion was placed in the rostral part of the lateral hypothalamic area. Anteriorly, it extends no further than the caudal end of the supraoptic nucleus where it forms a small area of damage reaching dorsally from the optic chiasma along the medial edge of this nucleus, and caudally it terminates at the rostral end of the ventro-medial nucleus. The medio-lateral extent of the lesion is similarly restricted, the direct damage to the lateral hypothalamus involving no more than the lateral half of this area (Fig. 7). The distribution of the degeneration in this brain is essentially similar to that described in experiment P16, but, as might be expected, the intensity of the degeneration is generally less marked. Considering the size of the lesion, the amount of degeneration in both the stria terminalis and the ventral hypothalamo-amygdaloid pathway is, however, surprising. That which enters the stria can be traced in continuity with the lesion forwards through the anterior hypothalamic area and thence dorsally into the stria itself. The degeneration passing into the ventral pathway extends laterally and forwards from the lateral aspect of the lesion through the lateral preoptic area into the anterior amygdaloid region. While the overall distribution of the preterminal degeneration in the amygdala is the same as in experiment P16 there are slight differences in its intensity in the different nuclei; the cortical nucleus contains rather more degeneration than in rat P16, but on the other hand, in the lateral and basal nuclei the amount of degeneration is somewhat less.

In view of the substantial amount of degeneration in the amygdala following involvement of the medial forebrain bundle at approximately the middle of its rostro-caudal extent in the hypothalamus, several lesions were placed at more caudal levels in the hypothalamus and in the rostral midbrain. Only two of these experiments will be described. In experiment MB8, a large electrolytic lesion was placed in the posterior part of the thalamus and the rostral midbrain, extending from the upper end of the habenulo-peduncular tract into the dorsal part of the ventral tegmental area and destroying most of the peri-aqueductal grey and the red nucleus back to the level of the oculomotor nucleus (Fig. 7). Although the caudal end of the medial forebrain bundle is not completely interrupted by this lesion, it is probable that most of the ascending fibres from the midbrain to this bundle have been divided (cf. Nauta and Kuypers, 1958; Cowan, Guillery, and Powell, 1964). Heavy fibre degeneration can be seen in the medial forebrain bundle (extending as far rostrally as the lateral preoptic area), the diagonal band, the medial septal nucleus, the dorsal fornix, the thalamus, and the zona incerta. No degeneration can be traced into the stria terminalis or into the ventral hypothalamo-amygdaloid pathway.

In experiment P13 there is a somewhat smaller lesion involving the medial forebrain bundle at the level of the mamillary nuclei. Apart from incidental damage by the electrode to the mediodorsal and habenular nuclei and part of the zona incerta, the main part of the lesion lies in the posterior hypothalamus where it destroys the lateral two-thirds of the lateral supra-mamillary region, the lateral mamillary nucleus, and the pars lateralis and pars posterior of the medial mamillary nucleus. Behind the mamillary nuclei, the lesion rapidly diminishes in size and ends near the ventral surface of the brain close to the point of emergence of the oculomotor nerve (Fig. 7). In this brain, again, there is no degeneration in the amygdaloid nuclei or in the two afferent pathways. Such negative evidence must of course be regarded with some caution, but the fact that in other sites in this brain degenerating fibres are well impregnated, makes it unlikely that the absence of fibre fragmentation in the stria terminalis or in the ventral pathway to the amygdala is due to technical factors.

In view of the evidence for a projection from the pyriform cortex to the medio-dorsal nucleus, and the possibility that this ventral pathway may also include amygdalo-thalamic fibres (Powell *et al.*, 1963), the possibility was considered that the mediodorsal nucleus might be a source of afferents to the amygdala as Nauta has recently described in the monkey (1962). It is, of course, extremely difficult to obtain lesions restricted to this nucleus in the rat but from several brains with lesions involving this nucleus, one will be described. In experiment H17 the lesion includes the stria habenularis and habenular nuclei, the medial part of the antero-dorsal nucleus and the parataenial and paraventricular nuclei together with the lateral two-thirds of the mediodorsal nucleus in its rostral half. Behind the middle of the mediodorsal nucleus, the lesion decreases rapidly in size and has not damaged its caudal pole (Fig. 7). From the inferior surface of the lesion degenerating fibres can be traced rostrally and ventrally, through the inferior thalamic peduncle, into the lateral preoptic area from which further degeneration can be traced laterally into the anterior amygdaloid area, rostrally into the diagonal band nucleus and the area

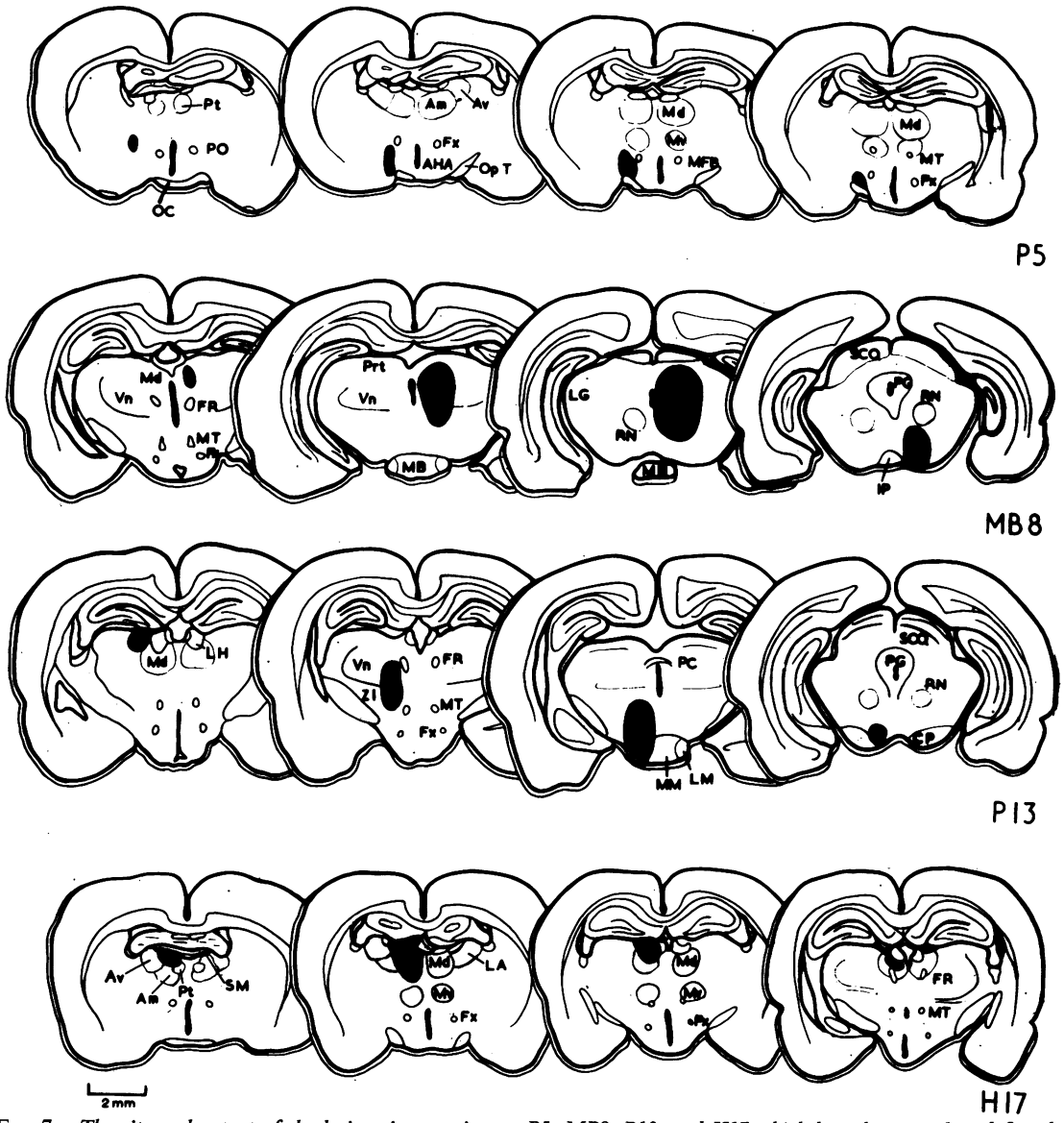


FIG. 7. *The site and extent of the lesions in experiments P5, MB8, P13, and H17 which have been used to define the limits of the diencephalic areas contributing afferent fibres to the amygdala.*

Pt	*parataenial nucleus of thalamus*
PO	*preoptic area*
OC	*optic chiasma*
Am	*antero-medial nucleus of thalamus*
Av	*antero-ventral nucleus of thalamus*
Fx	*fornix*
AHA	*anterior hypothalamic area*
OpT	*optic tract*
Md	*medio-dorsal nucleus of thalamus*
Mv	*medio-ventral nucleus of thalamus*
MFB	*medial forebrain bundle*
MT	*mamillo-thalamic tract*
Vn	*ventral nucleus of thalamus*
FR	*fasciculus retroflexus*
Prt	*posterior thalamus*
MB	*mamillary body*
LG	*lateral geniculate nucleus*
RN	*red nucleus*
SCQ	*superior corpus quadrigeminum*
PG	*periaqueductal grey*
IP	*interpeduncular nucleus*
LH	*lateral habenular nucleus*
ZI	*zona incerta*
PC	*posterior commissure*
MM	*medial mamillary nucleus*
LM	*lateral mamillary nucleus*
CP	*cerebral peduncle*
SM	*stria medullaris*
LA	*anterior part of lateral nucleus of amygdala*

between the olfactory tubercle and the striatum, and caudally through the medial forebrain bundle into the lateral hypothalamus. Other areas showing degeneration of fibres need not be enumerated, the important finding being that the principal amygdaloid nuclei and the stria terminalis are free of degeneration. This observation need not be regarded as contradicting Nauta's findings (1962) in view of the difficulties of homologizing different parts of the medio-dorsal nucleus in these two species, and because of the fact that even in the monkey, the thalamo-amygdaloid projection does not appear to be a heavy one.

The pattern of degeneration in the amygdala is essentially the same after interruption of the stria terminalis in its midcourse as in those brains in which the ventral pathway had also been interrupted. This is shown in experiment G7 where, following an electrolytic lesion in the dorso-lateral part of the thalamus which has completely divided the stria terminalis, numerous degenerating fibres can be traced caudally into the amygdala. There is a good deal of preterminal degeneration in the medial and cortical nuclei, and a little in the basal and lateral nuclei. Again degenerating fibres traverse the ventral part of the central nucleus, but it is difficult to be certain that any are terminating here. The distribution of the rostrally directed amygdalo-fugal fibres will not be described because of the concomitant damage to the fimbria.

To illustrate the total efferent projection of the amygdala a single representative experiment will be described. Experiment A8 has a large lesion in the amygdala with minimal damage to surrounding structures with the notable exception of the overlying pyriform cortex. Even in the absence of direct involvement of this cortex, it is impossible, in the rat, with any lesion of the baso-lateral amygdaloid nuclei, to exclude the interruption of efferent fibres from this cortical area (Powell *et al.*, 1965). The lesion in this experiment commences in the anterior amygdaloid area at the level of the interventricular foramen where it has also damaged the substantia innominata. Further caudally, the whole of the amygdala is destroyed with the exception of the narrow dorsal portion of the lateral nucleus (chiefly the lateral anterior nucleus). The lesion is bounded medially by the optic tract but extends laterally to involve a small portion of the pyriform cortex. Posteriorly, it narrows to a small defect which destroys the cortical amygdaloid nucleus (Fig. 8). The degenerating fibres leave the amygdaloid region in two distinct pathways, the stria terminalis and a ventral pathway along the base of the hemisphere. The stria terminalis shows coarse fibre fragmentation throughout its cross-sectional area, but this is most dense in its dorsal two-thirds. At the level rostral to the interventricular foramen, where the stria terminalis turns ventrally towards the anterior commissure, the fibres separate out into the various components which have been described in normal material. The contribution to the anterior commissure is clearly seen, and the degenerating fibres can be traced across the midline to the posterior limb of the commissure of the opposite side, where they run caudally in this bundle for a short distance; unfortunately, it has not been possible to determine their site of termination. A similar difficulty was encountered by Fox, Fisher, and DeSalva (1948), Hall (1960), and Nauta (1961) in their reports on this component. Most of the degenerating fibres of the stria pass ventrally either in front of, or behind, the anterior commissure to reach the medial preoptic area, where there is heavy pericellular fragmentation. Scattered degeneration continuous with this can be followed into the anterior hypothalamic area and as far caudally as the level of the hypothalamic ventromedial nucleus. The ventromedial and dorsomedial nuclei of the hypothalamus themselves are free of degeneration, but some fine fragments are seen along their lateral borders. Some of the precommissural degeneration passes forwards into the nucleus accumbens. Although there is a lot of preterminal degeneration around the cells of the bed nucleus of the stria terminalis, no degeneration can be seen in any of the nuclei of the septum.

In addition to the degenerating fibres which can be traced medially and dorsally into the stria, there is a more diffuse projection extending from the anterior amygdaloid area to several of the basal forebrain structures, the hypothalamus and the thalamus (Fig. 8). Traced rostrally, the degeneration extends into the lateral preoptic area, the nucleus of the diagonal band, and beneath the striatum to the olfactory tubercle and the neocortex on the medial aspect of the hemisphere. In each of these areas there is preterminal degeneration; in the nucleus of the diagonal band degeneration is found in both the horizontal and vertical limbs, but it becomes progressively less in the more medial parts of the nucleus; the degeneration in the olfactory tubercle is heavy and is found in all layers; rostral to the level of the septum, degenerating fibres can be traced into the cortex on the inferior part of the medial surface of the hemisphere to a level just rostral to the genu of the corpus callosum. Fibres pass medially through the lateral preoptic area and then caudally in the medial forebrain bundle back almost to the level of the mamillary nuclei. From the dorsal aspect of this pathway, numerous degenerating fascicles pass upwards and medially in the inferior thalamic radiation to reach the medio-ventral nucleus and the central

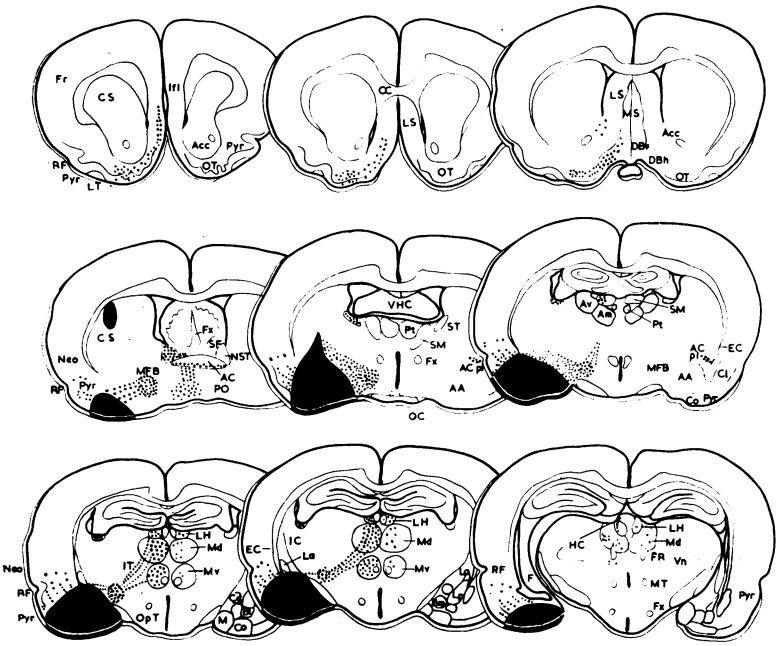


FIG. 8. *The site and extent of the lesion and the distribution of the degeneration in experiment A8.*

Fr	*frontal neocortex*
CS	*striatum*
RF	*rhinal fissure*
Pyr	*pyriform cortex*
LT	*lateral olfactory tract*
Ifl	*infralimbic cortex*
Acc	*nucleus accumbens*
OT	*olfactory tubercle*
CC	*corpus callosum*
LS	*lateral septal nucleus*
MS	*medial septal nucleus*
DBv	*vertical limb of diagonal band nucleus*
DBh	*horizontal limb of diagonal band nucleus*
Neo	*neocortex*
MFB	*medial forebrain bundle*
Fx	*fornix*
SF	*septo-fimbrial nucleus*
NST	*bed nucleus of the stria terminalis*
AC	*anterior commissure*
PO	*preoptic area*
VHC	*ventral hippocampal commissure*
Pt	*parataenial nucleus of thalamus*
ST	*stria terminalis*
SM	*stria medullaris*
ACpl	*posterior limb of anterior commissure*

AA	*anterior amygdaloid area*
OC	*optic chiasma*
Av	*antero-ventral nucleus of thalamus*
Am	*antero-medial nucleus of thalamus*
EC	*external capsule*
Cl	*claustrum*
Co	*cortical nucleus of amygdala*
IT	*inferior thalamic radiation*
OpT	*optic tract*
LH	*lateral habenular nucleus*
Md	*medio-dorsal nucleus of thalamus*
Mv	*medio-ventral nucleus of thalamus*
Ce	*central nucleus of amygdala*
Bl	*lateral part of basal nucleus of amygdala*
M	*medial nucleus of amygdala*
IC	*internal capsule*
La	*anterior part of lateral nucleus of amygdala*
Lp	*posterior part of lateral nucleus of amygdala*
Bm	*medial part of basal nucleus of amygdala*
F	*fimbria*
HC	*habenular commissure*
FR	*fasciculus retroflexus*
Vn	*ventral nucleus of thalamus*
MT	*mamillo-thalamic tract*

part of the mediodorsal nucleus. Here there is heavy preterminal degeneration but some of the fibres can be followed dorsally into the lateral habenular nucleus, where they end in a pericellular plexus. No attempt has been made to relate the components of the efferent projection of the amygdala to specific nuclei of origin, but evidence will be adduced to show that the ventral efferent pathway does not arise in the phylogenetically older cortico-medial group but that it either originates solely from the pyriform cortex or it may receive an additional contribution from the baso-lateral group of nuclei. In a group of four brains (A1, 2, 3, 4), lesions were placed in the cortical, medial, and central nuclei. The results

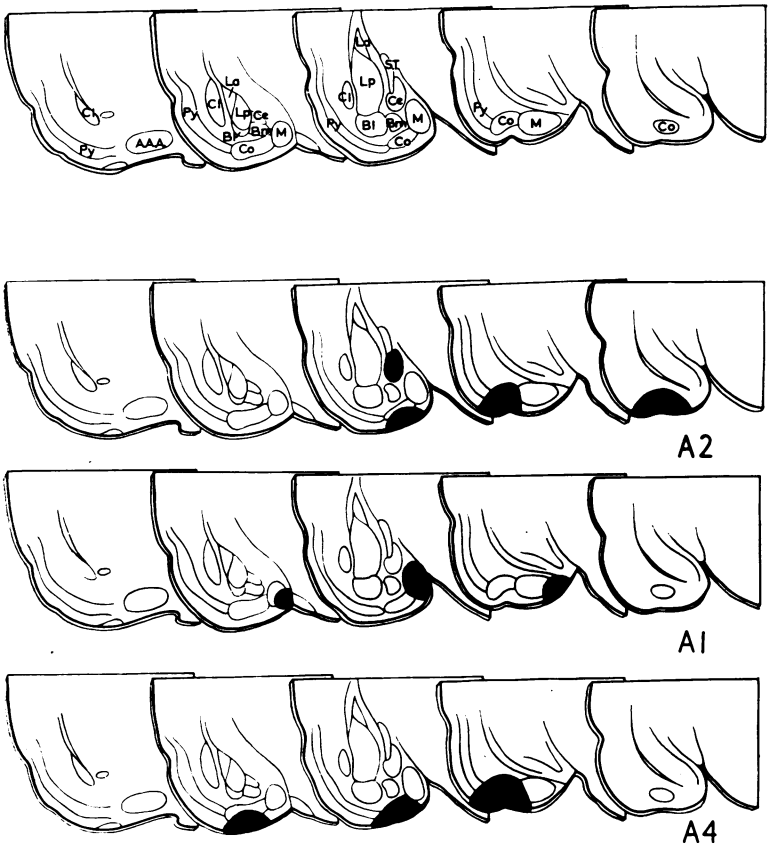


FIG. 9. *Outlines of coronal sections of the amygdaloid region to show the lesions in experiments A2, A1, and A4. The most rostral level is on the left and the most caudal on the right. The top row of outlines shows the different amygdaloid nuclei which are seen at the same rostro-caudal levels.*

Cl	*claustrum*
Py	*pyriform cortex*
AAA	*anterior amygdaloid area*
La	*anterior part of lateral nucleus of amygdala*
Lp	*posterior part of lateral nucleus of amygdala*
Ce	*central nucleus of amygdala*
Bm	*medial part of basal nucleus of amygdala*
M	*medial nucleus of amygdala*
Co	*cortical nucleus of amygdala*
ST	*stria medullaris*
Bl	*lateral part of basal nucleus of amygdala*

uniformly show degeneration in the stria terminalis but not in the ventral pathway, the mediodorsal nucleus, or the habenula. In experiment A2 the needle track traverses the neocortex and the lateral part of the striatum obliquely, damaging the central amygdaloid nucleus at the level of the middle of the thalamus, and then terminating as a small focus on the ventral surface of the hemisphere where it involves the posterior two-thirds of the cortical nucleus and a very small part of the pyriform cortex (Fig. 9). In experiment A1, the needle enters the brain more posteriorly and the track damages the stria terminalis and a small part of the lateral thalamic nucleus and caudally the lateral geniculate body. Reaching the base of the brain, a small focus of damage occurs in the inferior tip of the hippocampus, and the posterior half of the medial amygdaloid nucleus is selectively destroyed. There is no involvement of the pyriform cortex, and it is unlikely that any cortical efferent fibres are traversing the affected region in the medial tip of the hemisphere. The lesion in experiment A3 is very similar; the needle track is, however, negligible and does not traverse the stria terminalis, whereas the lesion additionally includes the posterior part of the cortical amygdaloid nucleus. Experiment A4 is also comparable, the needle traversing the striatum and the definitive lesion being restricted to the anterior two-thirds of the cortical amygdaloid nucleus without destroying any adjacent areas (Fig. 9). In all these brains, there is degeneration in the stria terminalis but not in the ventral pathway. The degeneration in the stria terminalis is distributed to those areas described for this bundle in experiment A8. Taken together, these brains exclude

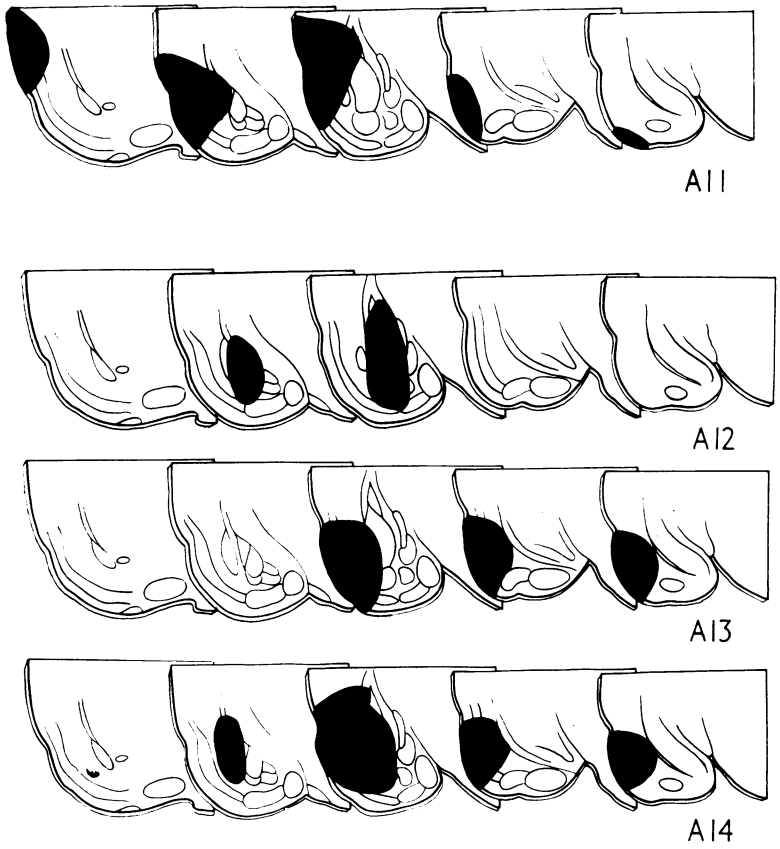


FIG. 10. *Coronal sections through the rostro-caudal extent of the amygdaloid region to show the extent of the lesions in experiments A11, A12, A13, and A14.*

the possibility of any fibres in the ventral pathway arising in the cortico-medial group of amygdaloid nuclei.

In another group of four brains (A11, 12, 13, 14) the lesion principally destroys the basolateral nuclei and gives rise to degeneration in both the stria terminalis and in the ventral amygdalo fugal pathway. In experiment A12 the lateral amygdaloid nucleus is completely destroyed together with the underlying basolateral nucleus. The central and basomedial nuclei are slightly damaged on their lateral sides, and a small lateral part of the cortical nucleus is damaged at more caudal levels where the lesion destroys the inferior tip of the pyriform cortex. The medial nucleus is unharmed (Fig. 10). Degeneration enters both the stria terminalis and the ventral pathway and terminates in the preoptic area, the medio-dorsal nucleus, and the lateral habenular nucleus. Its course and termination are similar to that described in experiment A8. The same degeneration occurs in experiment A13 where the lesion is much smaller, involving only the posterior part of the basolateral nucleus together with a small part of the pyriform cortex. Experiments A11 and A14 have lesions in both parts of the lateral nucleus and in the basolateral nucleus, with additional involvement of the overlying pyriform cortex (Fig. 10). Taken together, these four experiments indicate that the stria terminalis arises in part, at least, from the basolateral group of nuclei. Whether the degeneration found in the ventral pathway in these cases is due solely to the interruption of fibres from the pyriform cortex or whether the cells of the basolateral group do in fact contribute cannot be resolved. In all the experiments with larger lesions in the amygdala degeneration has been seen in the ipsilateral pyriform and adjoining temporal neocortical areas and in the posterior limb of the anterior commissure. Whether or not the amygdala contributes to one or all these components cannot be determined, as lesions in the amygdala inevitably involve the thalamo-cortical fibres passing laterally immediately above the amygdala, commissural fibres from the pyriform cortex, and direct olfactory afferents to the pyriform cortex. Fibres linking the amygdala with the temporal pole and insula have been described in

normal material and in an experimental study in the monkey (Nauta 1961). According to Nauta, these fibres reach the deep white matter of the inferior temporal gyrus and are distributed to the rostral parts of the middle and superior temporal gyri, the ventral insular cortex, the caudal part of the orbitofrontal cortex, and the claustrum.

DISCUSSION

AFFERENT CONNEXIONS Although it has long been recognized that the diencephalon represents the major projection field of the amygdala, the possibility that there may be a reciprocal relationship between these two regions has only been entertained seriously in the past few years. Older reports of caudally directed fibres in the stria terminalis, based on normal material, were clearly inconclusive and were not substantiated by the Marchi study of Fox (1943). There have been several recent descriptions, however, of the degeneration of fibres in the stria terminalis passing back to the amygdaloid nuclei (Nauta, 1958; 1962; Sanders-Woudstra, 1961; Shute and Lewis, 1961; Hilton and Zbrożyna, 1963; Valverde, 1963). In addition, there have been isolated reports of degenerating fibres passing from the region of the medial forebrain bundle to the amygdala (Nauta, 1962; Valverde, 1963), but there has been no suggestion that this ventral pathway may provide a second reciprocal connexion between the diencephalon and the amygdala.

The experimental observations in the present study have confirmed the previous accounts of caudally directed fibres to the amygdala in the stria terminalis, and in addition have demonstrated that the ventral pathway from the diencephalon, although more diffuse, is probably the larger. As far as can be assessed, both the dorsal and ventral amygdalopetal pathways have their origin in the rostral half of the hypothalamus, and although a small contribution may be derived from more caudal areas, experiments with lesions in the caudal hypothalamus, rostral midbrain, and medial thalamus did not result in detectable degeneration in these pathways. Similarly, both pathways probably end in the same region, as selective lesions of the stria terminalis in its mid-course result in the same pattern of degeneration as when both pathways are involved. It appears that all of the amygdaloid nuclei, with the exception of the central nucleus, are in receipt of diencephalic afferents, and it is noteworthy that this corresponds to the total olfactory input to the amygdala, as will be shown later. From its site of origin and its course through the preoptic area the ventral pathway may be regarded as a rostral and lateral continuation of the medial forebrain bundle into the amygdala. In this case the anterior amygdaloid area should be considered as a bed nucleus for the amygdaloid component of the medial forebrain bundle in much the same way as the cells of the lateral hypothalamic and lateral preoptic areas constitute a bed nucleus for its hypothalamic and preoptic parts respectively. It may also be helpful to consider the stria terminalis as a displaced component of the medial forebrain bundle which has become topographically separated from the rest of that bundle by the fibres of the internal capsule.

The existence of an important projection to the amygdala from the olfactory bulb has been accepted for some time, and has found experimental support in the studies of Le Gros Clark and Meyer (1947), Meyer and Allison (1949), and Allison (1953) using the Glees technique. These authors have described two pathways from the olfactory bulb to the amygdala in several species; the first, in the lateral olfactory tract to the cortical and medial nuclei, and the second, a bilateral pathway, through the anterior limb of the anterior commissure, to the central amygdaloid nucleus and the bed nucleus of the stria terminalis. More recent studies, however, using the Nauta technique, have questioned the existence of a projection through the anterior commissure and have pointed to a much more limited termination within the amygdaloid nuclei. For example, Sanders-Woudstra (1961), Cragg (1961), and Lohmann (1963) could trace degenerating fibres in the lateral olfactory tract only to the nucleus of the tract and to the region of the cortical amygdaloid nucleus. This more limited olfactory representation in the amygdala is in agreement with the electrophysiological studies of Adrian (1942) and of Rose and Woolsey (1943), and with the findings of several comparative anatomical studies (Addison, 1915; Langworthy, 1932; Breathnach and Goldby, 1954).

A detailed study of the projection of the olfactory bulb has been presented elsewhere (Powell *et al.*, 1965) and only the findings relevant to the amygdaloid nuclei will be summarized here. After unilateral removal of the main and accessory olfactory bulbs degenerating fibres can be traced in the lateral olfactory tract to the nucleus of this tract, the periamygdaloid cortex, and the cortical and medial amygdaloid nuclei. The amount of degeneration found in the amygdaloid nuclei becomes progressively less both caudally and medially. No degeneration has been found in the central amygdaloid nucleus nor in its supposed continuation, the bed nucleus of the stria terminalis on either side of the brain. Degenerating fibres are only seen in the anterior commissure when the anterior olfactory nucleus is involved in addition to the olfactory bulb,

but even in such cases the central amygdaloid nucleus is free of degeneration.

It may be concluded, therefore, that although there is a direct projection from the olfactory bulb to the amygdala, it appears to be less extensive than has generally been assumed. All the reports based upon the use of the Nauta method, with the exception of Johnson's (1959), are in agreement that the central amygdaloid nucleus does not receive fibres from the olfactory bulb via the anterior commissure. One possible explanation for the discrepancy between these observations and those in which the Glees method was used is that the latter method is now known to give pseudo-degeneration in such sites as the bed nucleus of the stria terminalis and certain parts of the hypothalamus (Cowan and Powell, 1956).

Several authors have described a pathway from the olfactory tubercle to the amygdala in normal material, but, with the exception of Pribram, Lennox, and Dunsmore (1950), who obtained responses in the amygdala on strychninization of the olfactory tubercle, there has been no experimental evidence for such a connexion. It is extremely difficult to investigate this problem with degeneration techniques because it is virtually impossible to place selective lesions in the olfactory tubercle without damaging either the medial part of the pyriform cortex or the deep projection from the olfactory bulb. In several of our rat experiments the medial part of the tubercle has been involved as part of a larger lesion placed primarily in the other hemisphere, and although there is definite degeneration in other fibre tracts in these sections, no degenerating fibres can be seen passing from the damaged medial part of the tubercle to the amygdala (unpublished observations). As regards the problem whether the olfactory tubercle, as a whole, is projecting to the amygdala, such negative observations are obviously inconclusive. It would be more significant to know if the antero-lateral part of the tubercle is connected to the amygdala as it is this part which is in receipt of olfactory afferent fibres.

Afferents to the amygdala by way of the longitudinal association bundle from the pyriform cortex have been described in normal material by many authors, and there is some experimental evidence based on strychnine neuronography (Pribram *et al.*, 1950) and the Marchi method (Ban and Omukai, 1959). There have also been suggestions that the neocortex immediately above the rhinal sulcus may contribute to this pathway (Whitlock and Nauta, 1956; Segundo, Naquet and Arana, 1955). In a recent experimental study of the pyriform cortex using the Nauta method (Powell *et al.*, 1965) it was found that the whole area of the pyriform cortex sends fibres to the basal and lateral amygdaloid nuclei. Following small, superficial lesions of the anterior part of the pyriform cortex heavy fibre degeneration can be traced caudally through the lateral amygdaloid area to the basal and lateral amygdaloid nuclei and in these there is clear evidence of preterminal fibre fragmentation. After lesions of more caudal parts of the pyriform cortex degenerating fibres pass directly medially and forwards through the amygdala to reach the lateral preoptic area, and again there is definite evidence that some fibres terminate in the basal and lateral amygdaloid nuclei. Control lesions in the neocortex immediately adjoining the rhinal sulcus and in the cortex of the entorhinal area do not give degeneration in any of the amygdaloid nuclei. In addition to this direct projection to the amygdaloid nuclei, the pyriform cortex is connected with areas such as the lateral preoptic region and hypothalamus which, as has been shown, are reciprocally connected with the amygdaloid nuclei.

The significance of these findings is that they provide an indirect, but nonetheless substantial, olfactory influence upon the amygdaloid nuclei. It is of interest that this indirect olfactory pathway terminates in different components of the amygdaloid complex from those receiving olfactory fibres directly through the lateral olfactory tract, and it appears that the two pathways together influence all the amygdaloid complex except the central nucleus.

EFFERENT CONNEXIONS The findings on the total projection of the amygdala are in general agreement with those of most other workers in this field (Fox, 1943; Lammers and Lohman, 1957; Hall, 1960; and Nauta, 1961), but before discussing this projection in detail, it is necessary to consider the recent evidence on the efferent connexions of the pyriform cortex (Powell *et al.*, 1963). The entire pyriform cortex not only sends fibres into and through the amygdaloid region as discussed above but the further course and distribution of this projection is precisely the same as that described for the ventral amygdalofugal pathway. On the other hand the pyriform cortex does not contribute to the stria terminalis as Cajal (1911) suggested, and it may be accepted therefore that the rostrally directed fibres in the stria are exclusively amygdaloid efferents. The evidence from the experiments with localized amygdaloid lesions make it clear that the stria arises from both the corticomedial and baso-lateral groups of nuclei. As regards the termination of the stria, it is doubtful whether the division of this bundle into separate components is really of value as the greater part of its projection is into the preoptic region, and the course of the fibres rostral or caudal to the anterior

commissure is probably only of topographical significance. The present observations are in agreement with those of Nauta (1961) in restricting the projection of this part of the stria terminalis to essentially the medial preoptic and anterior hypothalamic areas with no contribution to the ventromedial or dorsomedial hypothalamic nuclei as described by Adey and Meyer (1952) and Adey, Rudolph, Hine, and Harritt (1958). The findings of these authors, based upon the Glees technique, are adequately accounted for by the misinterpretation of the pseudo-degeneration which is now well known to occur in these nuclei (Cowan and Powell, 1956; Szentagothai, 1962). In this connexion it may be pointed out that a feature of all the genuine fibre degeneration in the hypothalamus is the fact that it is found in the lateral or dorsal hypothalamic areas, and that with the exception of the mamillary nuclei it is never observed in the well-differentiated medial nuclei. As Szentagothai (1962) has suggested, this may well be due to the fact that the terminal parts of the afferent fibres to these nuclei are too fine to be demonstrable with conventional neurohistological methods for axonal degeneration.

It is not possible, for the reasons already given, to determine with certainty whether the ventral pathway receives fibres from the amygdala in addition to those which arise in the pyriform cortex. If there is an amygdaloid projection to this pathway, however, it must arise solely from the baso-lateral group of nuclei as lesions restricted to the cortico-medial group of nuclei have not shown degeneration in the ventral pathway. Several indirect lines of evidence may be suggested in support of such an origin. For example, as the stria terminalis is known to convey both amygdalo-petal and amygdalo-fugal fibres, it might be expected, on *a priori* grounds, that the second major pathway would similarly contain amygdaloid efferents as well as afferent fibres. Furthermore, it appears to be a common feature of cortical areas to send fibres both directly and indirectly to their projection field, and by analogy it might be argued that the pyriform cortex is related to the diencephalon both directly and indirectly through the baso-lateral amygdaloid nuclei. Although the ventral pathway, as a whole, has an extensive distribution to the basal forebrain areas, the hypothalamus, thalamus, and epithalamus, it should not be assumed that any possible amygdaloid contribution to this pathway necessarily projects to all these sites. Indeed, in view of the relatively limited distribution of the stria terminalis such a widespread projection would seem unlikely.

GENERAL CONCLUSIONS The primary purpose of this study was to attempt a synthesis of the known afferent and efferent connexions of the amygdala, and to present further observations bearing upon their organization. The afferent connexions may be classified in general terms as being either olfactory or diencephalic. The olfactory afferents are either direct or indirect with respect to the olfactory bulb; the direct come through the lateral olfactory tract, and, terminating within the cortico-medial group, have a more restricted distribution than was formerly thought. The indirect olfactory pathway forms part of the longitudinal association bundle arising from all parts of the pyriform cortex and terminating within the basal and lateral nuclei. Thus, although the direct projection of the olfactory bulb to the amygdala is more restricted than was previously considered, all the amygdaloid nuclei, with the exception of the central, must be included as part of the central olfactory projection. The precise site of origin of the diencephalic afferents is not known, but the evidence available at present points to the rostral half of the hypothalamus as being the most probable source. These afferents similarly reach the amygdala by two distinct pathways of different size; the smaller of these is represented by the caudally directed fibres in the stria terminalis, and the larger and more diffuse passes directly to the anterior amygdaloid area beneath the internal capsule. As far as can be determined the fibres terminate in the same nuclei, and, again, all but the central are included.

The efferent connexions of the amygdala are directed primarily to the diencephalon, and while all the nuclei appear to contribute to the stria terminalis only those of the baso-lateral group may send fibres into the ventral pathway. For technical reasons it is not possible to determine the magnitude of the amygdaloid contribution to the ventral pathway, and, as a large part of this fibre tract is known to arise in the pyriform cortex, it is likely that much of what has hitherto been accepted as an amygdalofugal pathway is, in fact, a projection system of fibres from the pyriform cortex. As the majority of the efferent fibres in both the stria terminalis and the ventral pathway are ending in the rostral hypothalamus, it is clear that this part of the hypothalamus is both receiving fibres from and also sending fibres to the amygdala. This reciprocal amygdalo-hypothalamic relationship is perhaps the most interesting finding of the present study, and it suggests that the ventral pathway is really a lateral extension, into the telencephalon, of the medial forebrain bundle, with the anterior amygdaloid area serving as a bed nucleus for this part of the bundle. This concept of the ventral pathway is in agreement with the suggestion that the stria terminalis represents a displaced dorsal part of the medial forebrain bundle which has become separated off by the

development of the internal capsule (Johnston, 1923).

It is not the intention of this paper to discuss the extensive literature on the physiology of the amygdala as this has been dealt with at length in the critical review of Gloor (1960). From a functional point of view the amygdala appears to be particularly concerned with the regulation of reproductive and affective behaviour, and for both of these it is now known that olfactory mechanisms play a dominant role, at least in many lower mammals (cf. Parkes and Bruce, 1961). To some extent the present observations provide an anatomical basis for this regulatory role as it appears that the amygdala is in a position to sample, either directly or indirectly, all olfactory afferents to the hypothalamus. Undoubtedly, the major olfactory input to the hypothalamus is directly through the pyriform cortex, but, on the basis of its connexions, the amygdala could well be the site of interaction of olfactory and hypothalamic activity. This relationship between the amygdala and pyriform cortex is reminiscent, in some respects, of that between the corpus striatum and the neocortex, and also of that between the septum and hippocampus. It is now known that the striatum is a site of interaction between the outflow of the entire neocortex and the ascending connexions from the thalamus (Powell and Cowan, 1956; Carman, Cowan, and Powell, 1963). Similarly, the septum provides for the interaction of ascending activity from the hypothalamus and midbrain to the hippocampus with the descending projection of the hippocampus to the diencephalon (Guillery, 1957). It is tempting to generalize from these examples and say that each cortical area of the forebrain is related, in a similar manner, to a subcortical integrative centre, and it may well be that the elucidation of the functional role of any one of these subcortical regions may throw considerable light on the significance of the others.

One outstanding question which these studies on the amygdala have only served to emphasize is that of the meaning of architectonic differentiation. This is a problem in nearly all sites in the central nervous system, but it is particularly obvious in the amygdala, where there are no fewer than seven architectonically distinct nuclei and apparently only two major sources of afferent connexions (from the olfactory bulb and hypothalamus) and a common outflow to the diencephalon. At present it is possible to account for some of these differences on the basis that the two major groups of nuclei (the cortico-medial and the baso-lateral) have differential connexions, and it is probable that closer analysis may show important differences within these two groups. An analogy may be drawn here with the mamillary nuclei, where it is now known that each of the morphological subdivisions receive differential connexions from the hippocampus and midbrain, and send their efferents to different components of the anterior thalamic nuclei or to the midbrain tegmentum (Powell, 1959).

SUMMARY

The afferent and efferent connexions of the amygdala have been studied in the rat using the Nauta technique. The afferent connexions may be considered as either diencephalic or olfactory; the diencephalic afferents are derived principally from the rostral hypothalamus, and reach the amygdala through both the stria terminalis and a lateral extension of the medial forebrain bundle, the ventral amygdalo-petal pathway, to terminate in all but the central nucleus. The olfactory afferents are both direct and indirect, from the olfactory bulb and pyriform cortex respectively. The direct afferents pass through the lateral olfactory tract to the nucleus of the lateral olfactory tract, the cortical and medial nuclei; and the indirect, from the pyriform cortex, join the longitudinal assocation bundle and are distributed to the basal and lateral amygdaloid nuclei. The efferent projection of the amygdala is mainly to the preoptic areas and hypothalamus. Both the cortico-medial and baso-lateral group of nuclei contribute to the stria terminalis, but whether the baso-lateral nucleus also contributes fibres to the ventral pathway cannot be determined in view of the proximity of fibres from the pyriform cortex which are known to form the major component of this pathway.

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