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NEURAL INPUTS INTO THE NUCLEUS BASALIS OF THE SUBSTANTIA INNOMINATA (Ch4) IN THE RHESUS MONKEY

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SUMMARY

Neurons of the nucleus basalis-substantia innominata-nucleus of the ansa peduncularis complex (Ch4) provide the major source of cholinergic innervation for the entire neocortical surface. In contrast to their widespread projections to all parts of the neocortex, these neurons receive reciprocal projections from only very few cortical areas. Most of the sensory, motor, and association areas in the frontal, parietal, occipital and temporal lobes do not seem to project back to the Ch4 complex. The Ch4 neurons receive their cortical input from prepyriform cortex, orbitofrontal cortex, the anterior insula, the temporal pole, entorhinal cortex and the medial temporal cortex. There are also subcortical inputs from septal nuclei, the nucleus accumbens-ventral pallidum complex and the hypothalamus. This organization suggests that the Ch4 complex is in a position to act as a cholinergic relay for transmitting predominantly limbic and paralimbic information to the neocortical surface. It would also appear that the cortical areas which do not project into Ch4 have no direct way of controlling the cholinergic input which they receive, whereas the limited set of cortical areas which do project into Ch4 can control not only the cholinergic innervation that they receive but also the cholinergic innervation into the entire neocortical mantle.

INTRODUCTION

Extensive pathological alterations have been reported in the nucleus basalis of Meynert in a number of neuropsychiatric conditions ranging from Alzheimer's disease to schizophrenia (Whitehouse *et al.*, 1981; Stevens, 1982). This nucleus is the most conspicuous constituent of a complex region in the basal forebrain which is variably referred to as the subcommissural grey, the sublenticular region, the anterior perforated substance or the substantia innominata. The large and hyperchromic neurons of the nucleus basalis extend from the level of the septum and olfactory tubercle to the level of the lateral geniculate nucleus. These neurons form discontinuous cell islands and intermingle with the fibre bundles of the ansa lenticularis, the ansa peduncularis, the inferior thalamic peduncle, the internal

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capsule, the anterior commissure, the medullary laminae of the globus pallidus and the medial forebrain bundle (Mesulam *et al.*, 1983*a*). Meynert (1872) is credited with the first microscopic description of this nucleus which he named the ganglion of the ansa peduncularis. Since then, several more extensive descriptions of this nucleus have been published (Kölliker, 1896; Foix and Nicolesco, 1925; Papez and Aronson, 1934; Mettler, 1942; Riley, 1943; Gorry, 1963). However, there has been little agreement with respect to the nomenclature for this complex nucleus. Following the designation 'ganglion of the ansa peduncularis' which was introduced by Meynert, terms such as the nucleus basalis, the nucleus of the ansa lenticularis, the nucleus of the septal plane, the preoptic magnocellular nucleus and the substantia innominata have also been used to designate essentially the same assembly of neurons in the primate brain (Papez and Aronson, 1934; Gorry, 1963). It is uncertain whether these terms were intended to designate exactly identical groups of neurons or if, as is far more likely, they referred to overlapping but different portions of the same overall nuclear complex. Perhaps the difficulty in reaching a more uniform nomenclature may be attributed to the organization of the constituent neurons into widely separated islands and to their incomplete demarcation either from adjacent nuclear groups or from the many fibre bundles which traverse the basal forebrain.

Recent advances have considerably reduced the ambiguities inherent in the delineation of the neurons which belong to the nucleus basalis-substantia innominata-ansa peduncularis complex. In the Rhesus monkey, at least 90 per cent of these neurons contain acetylcholinesterase as well as choline acetyltransferase (Mesulam and Van Hoesen, 1976; Poirier *et al.*, 1977; Mesulam *et al.*, 1983*a*). This cytochemical pattern distinguishes the basalis-substantia innominata-ansa peduncularis complex from the adjacent neurons of the globus pallidus, the preoptic region, the lateral hypothalamic area and the amygdaloid complex, none of which contains choline acetyltransferase-positive neurons. A second characteristic of the basalis-substantia innominata-ansa peduncularis complex is its widespread projections to the entire neocortical surface which makes it the major source of the cholinergic innervation in neocortex (Divac, 1975; Kievit and Kuypers, 1975; Mesulam and Van Hoesen, 1976; Mesulam *et al.*, 1983*a*, *b*; Pearson *et al.*, 1983*b*). This pattern of connectivity sets this nuclear complex apart from adjacent cholinergic neurons of the diagonal band nuclei and of the striatum which do not have extensive neocortical projections.

In order to reduce some ambiguities with respect to the nomenclature currently applied to this region, we proposed the designation Ch1 to Ch4 for the four groups of cholinergic projection neurons in the basal forebrain of monkeys and humans (Mesulam *et al.*, 1983*a*). In this nomenclature, the Ch1 to Ch3 groups correspond to the cholinergic neurons located in the medial septum (Ch1) and within the vertical (Ch2) and horizontal (Ch3) limb nuclei of the diagonal band. The designation Ch4 was proposed as a collective term for the entire assembly of choline acetyltransferase-positive neurons which preferentially project to the neocortical mantle and the amygdala. Defined in this manner, the Ch4 group contains neurons

which are usually included in the nucleus basalis of Meynert, the substantia innominata, the nucleus of the ansa lenticularis and the nucleus of the ansa peduncularis. The extensive Ch4 complex was further subdivided into anteromedial (Ch4am), anterolateral (Ch4al), intermediodorsal (Ch4id), intermedioventral (Ch4iv) and posterior (Ch4p) sectors, each with a preferential set of neocortical regions as the target for its projections (Mesulam *et al.*, 1983*a*, *b*).

The limited information on the behavioural specializations of the Ch4 complex does suggest that these neurons have response contingencies which go beyond simple sensory processing or motor control. In contrast to the neurons of the globus pallidus which change their rate of firing in temporal relationship to push-pull movements of the limbs and which undoubtedly play an important role in motor control, the adjacent neurons of Ch4 (substantia innominata) in the macaque responded to the delivery of a juice reward (DeLong, 1971). These neurons also responded to the sight and taste of food. The magnitude of this response was influenced by the desirability of the food object and also by the animal's state of hunger (Burton *et al.*, 1975; Rolls *et al.*, 1979). These observations suggest that the Ch4 neurons are especially responsive to motivational states and that they must be receiving an extensive array of sensory and limbic inputs which enables them to associate external sensory events with internal drive states. The pattern of this input influences the type of information processing which occurs in Ch4 and is of considerable importance in unravelling the behavioural specializations of this region.

Neuroanatomical experiments in the macaque have shown the presence of neural projections into Ch4 from the amygdala, the medial frontopolar cortex, the ventromedial hypothalamic nucleus, the magnocellular portion of the dorsomedial nucleus of the thalamus, caudal orbitofrontal cortex and the peripeduncular nucleus (Nauta and Haymaker, 1969; Jones *et al.*, 1976; Leichnetz and Astruc, 1977; Saper *et al.*, 1979; Price and Amaral, 1981). The purpose of this paper is to provide a more extensive analysis of neural inputs into Ch4 and to investigate how the distribution of this input corresponds to the topography of efferent connections from Ch4 to the neocortical mantle.

METHODS

Thirty-seven Rhesus monkey cerebra were available for investigating the neural inputs into the basalis-substantia innominata-ansa peduncularis complex (Ch4). In each animal, an injection of tritiated (^{3}H) amino acids (TAA) was made within cortical or subcortical targets. The injectate consisted of a mixture of ^{3}H-amino acids including proline, lysine and leucine. In each case, the injected volume ranged from 0.1 to 0.4 μl and contained 10 to 50 μCi of radioactivity. For cortical targets, the desired area was exposed directly through a craniotomy. Subcortical targets were reached stereotaxically. All injections were made through a microsyringe attached to a stereotaxic microdrive. Following a survival period of five to ten days, the animal was deeply anaesthetized and perfused transcardially first with saline and then with aldehydes. This range of survival times yields optimal visualization of efferent projections in the Rhesus monkey. The brain was then removed, embedded in paraffin and processed for autoradiography according to the recommendations of Cowan *et al.* (1972).

In essence, the tissue sections were coated with a photosensitive emulsion (Kodak NTB-2), exposed in total darkness at −80° C for 18 to 145 weeks, developed in Kodak D-19 and then fixed and counterstained lightly with thionin. The beta radiation from the TAA causes a precipitation of the silver in the emulsion. Regions that contain the TAA can therefore be identified by the presence of dense silver grains. These grains will be referred to as 'label' in the following text.

The autoradiographic tracing of neural connections with TAA injections has introduced marked improvements in investigating the efferent projections of neurons. The injected TAA are taken up into the perikarya at the injection site, incorporated into newly synthesized protein and transported anterogradely into the axons and terminals in the rapid phase of active transport. Following an appropriate survival time and with the help of the autoradiographic procedures described above, the axons and terminal projection fields of the perikarya within the injection site can be detected by the presence of the silver grain label. The axons that are passing through the injection site do not contribute to the final pattern of labelling since they are not capable of synthesizing new protein even if the injected TAA did find access into the axoplasm. The final pattern of labelling therefore provides a relatively selective map of the efferent projections only of the perikarya situated within the injection site.

In our experiments, the TAA injection site was defined as the region which contained uniformly dense precipitates of label over the neuropil as well as over the perikarya. In each case, all sections through the Ch4 region were examined microscopically with dark-field illumination in order to detect the labelling due to the anterogradely transported TAA. The presence of nonlinear and relatively homogeneous clusters of label within Ch4 was interpreted to indicate labelling within the terminal axonal fields. Cases which contained this pattern of labelling were considered positive with respect to a projection from the injection site to Ch4. Only labelling which was markedly more intense than the background level was taken into consideration. Ch4 labelling predominantly arranged in linear streaks was attributed to passing fibres and not considered to represent a projection from the injection site. When a case was free of label in Ch4, we determined whether it contained the expected anterograde labelling in the striatum or the claustrum before concluding that the neurons in the injection site of that case did not project to Ch4. This allowed us to ascertain that the negative results could not be attributed to the lack of uptake and transport from the injection site, to insufficient exposure time or to technical difficulties in development, fixation and counterstaining.

RESULTS

The anterior part of Ch4 is located just behind the level of the olfactory tubercle, at a point where the anterior commissure crosses from one hemisphere to the other. This anterior sector can be subdivided into a lateral (Ch4al) segment which abuts on the anterior amygdaloid area and a medial (Ch4am) segment which is adjacent to the vertical limb nucleus of the diagonal band (fig. 1). Further caudally, at the level where the anterior commissure loses its continuity, the intermediate sector of Ch4 (Ch4i) can be identified. The ansa peduncularis separates Ch4i into dorsal (Ch4id) and ventral (Ch4iv) subdivisions. Behind the ansa peduncularis, there is the posterior sector of Ch4 (Ch4p) which is surrounded by the globus pallidus, optic tract and putamen (fig. 1). At each level, Ch4 also has interstitial neurons which surround or even penetrate the fibre bundles of the internal capsule, the anterior commissure, the inferior thalamic peduncle and the medullary laminae of the globus pallidus. The identity of these neurons as members of the Ch4 complex is easily determined by their positivity for choline acetyltransferase and their connections with neocortex (Mesulam *et al.*, 1983*a*).

Frontal Lobe TAA Injections

In 9 of the animals (Cases 1 to 9), the TAA injection was made within parts of the frontal lobe (fig. 2). In Cases 1 to 5 the injection site was located within portions of dorsolateral frontal cortex in areas 8, 10, 45 and 46 of Walker (1940) and area 6 of Brodmann (1905). These cases did not contain terminal field labelling in the basalis-substantia innominata-ansa peduncularis complex (Ch4). Cases 6 to 9 were positive in a pattern which was consistent with terminal field labelling within Ch4. In Cases 6 and 7 where the injection site was centred in the lateral part of the orbitofrontal area 12 of Walker, the Ch4 labelling was especially intense in Ch4i (Table). The injection site in Cases 8 and 9 was within the caudal orbitofrontal area 13 of Walker. In these cases, Ch4 labelling was particularly intense in Ch4al and Ch4i (fig. 4). The injection site extended slightly into the claustrum in Case 9 but not in Case 8.

Parietal and Occipital Lobe TAA Injections

In Cases 10 to 14, the injection sites were located within the postcentral gyrus (area 2), the superior parietal lobule (area 5), the inferior parietal lobule (area 7), the medial posterior parietal cortex and the peristriate cortex (fig. 2). None of these cases contained Ch4 labelling above the background level.

Temporal Lobe TAA Injections

Injections that were confined to portions of the auditory association cortex (area TA of Bonin and Bailey (1947) or 22 of Brodmann), in the middle and caudal parts of the superior temporal gyrus (Cases 15 and 16) and those in the visual association cortex (area TE of Bonin and Bailey or 21 of Brodmann) of the middle temporal gyrus (Case 17), did not yield terminal field labelling in Ch4. In Cases 18 and 19 the injection sites were located within portions of the posterior parahippocampal gyrus (area TF-TH of Bonin and Bailey). Of these 2 animals, Case 18 was considered negative because the great majority of Ch4 labelling was in the form of linear streaks and therefore within passing fibres rather than in terminal fields (fig. 5). Case 19 may have contained nonlinear Ch4 labelling slightly above the background level but this could not be established with confidence. In Case 22 which had a TAA injection within the hippocampal formation, terminal labelling was intense in the septal and diagonal band areas but not in Ch4 (fig. 3 and Table).

Cases 20, 21 and 23 to 25 each had substantial Ch4 labelling in a pattern which was consistent with terminal field labelling. The injection site in Case 20 was centred within the medial portion of the inferotemporal visual association cortex (area TEm of Turner *et al.* (1980)) with a minor extension into the perirhinal cortex of Van Hoesen and Pandya (1975). In Case 21, the injection site was confined to entorhinal cortex. In both these animals (Cases 20 and 21), substantial labelling occurred in Ch4al and Ch4i, with a relative peak in the latter subdivision (Table and fig. 6).

[*Text continues on p. 265.*]

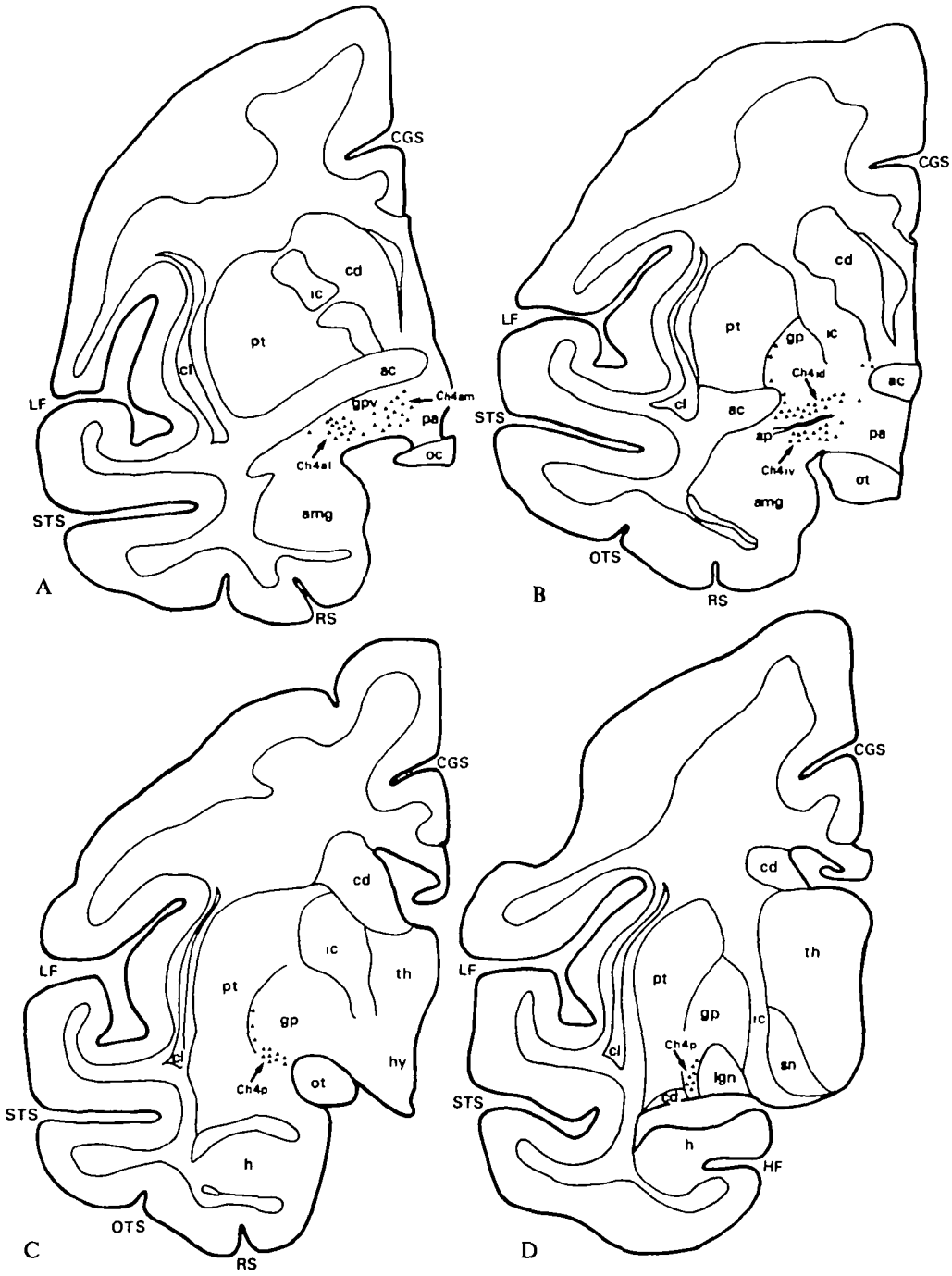

FIG. 1. Location of Ch4 sectors in the Rhesus monkey. Diagrams A–D illustrate sections at progressively more caudal levels of the brain.

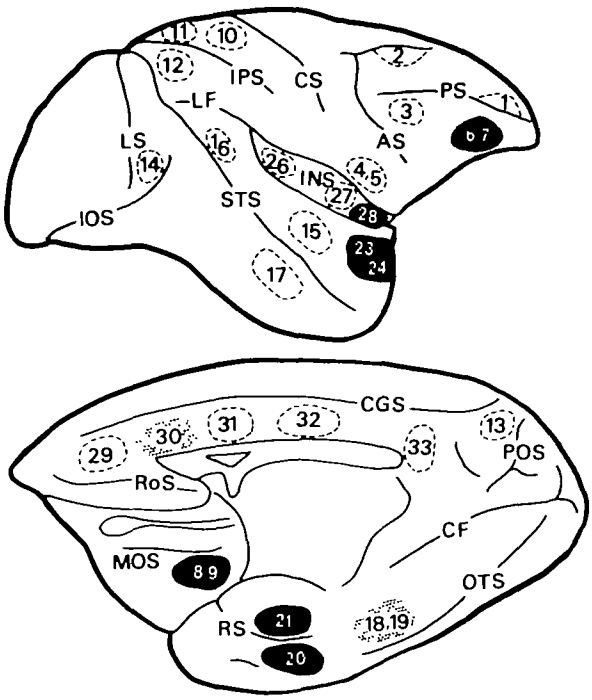

FIG. 2. Representation of the TAA injection sites. The numbers correspond to the case numbers in the Table and in the text. Injection sites surrounded by broken lines indicate cases without Ch4 labelling. Injection sites marked by the black areas indicate cases with positive Ch4 labelling. Cases with questionable Ch4 labelling are indicated by light stippling. *Upper*, lateral aspect of the hemisphere. *Lower*, medial and basal aspects of the hemisphere.

List of abbreviations

ac	anterior commissure
amg	amygdala
ap	ansa peduncularis
AS	arcuate sulcus
cd	caudate
CF	calcarine fissure
CGS	cingulate sulcus
Ch4al	anterolateral division of cholinergic cell group 4
Ch4am	anteromedial division of cholinergic cell group 4
Ch4id	intermediodorsal division of cholinergic cell group 4
Ch4iv	intermedioventral division of cholinergic cell group 4
Ch4p	posterior division of cholinergic cell group 4
cl	claustrum
cs	central sulcus
gp	globus pallidus
gpv	ventral globus pallidus
h	hippocampus
HF	hippocampal fissure
hy	hypothalamus
ic	internal capsule
INS	insula
ios	inferior occipital sulcus
IPS	inferior parietal sulcus
LF	lateral fissure
lgn	lateral geniculate nucleus
LS	lunate sulcus
LSA	lateral septal area
MHY	medial hypothalamus
MOS	medial orbital sulcus
MS	medial septal area
NA	nucleus accumbens
NVL	nucleus of the vertical limb of the diagonal band
oc	optic chiasma
ot	optic tract
OTS	occipitotemporal sulcus
pa	preoptic area
POS	parieto-occipital sulcus
PS	principal sulcus
pt	putamen
PYR	prepyriform cortex
ROS	rostral sulcus
RS	rhinal sulcus
sn	substantia nigra
sts	superior temporal sulcus
th	thalamus
V	ventricle

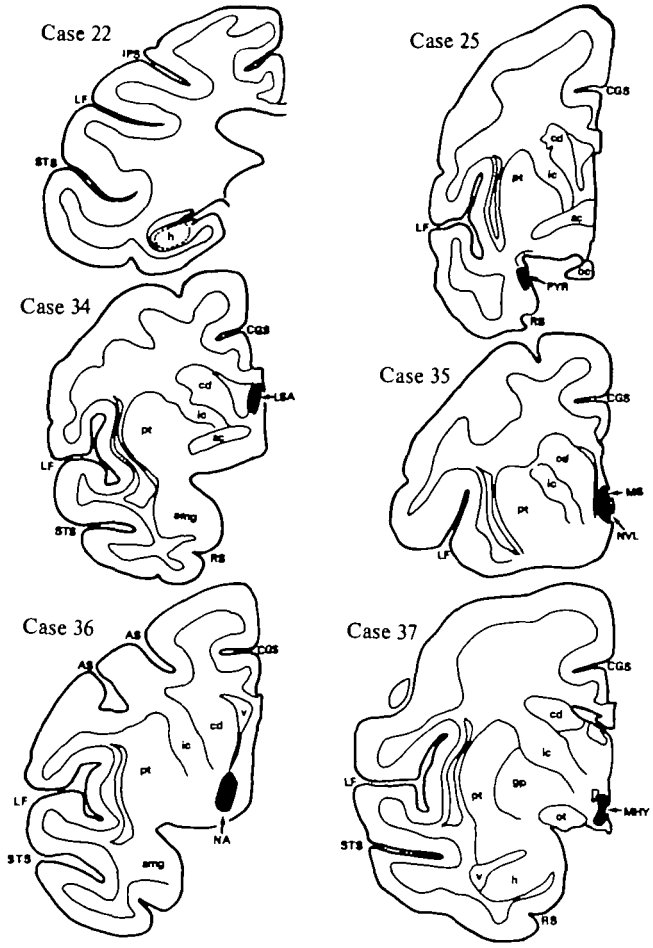

FIG. 3. Representation of the TAA injection sites. Case numbers are the same as those in the Table and in the text. The injection site surrounded by broken lines in Case 22 indicates that this case did not have Ch4 labelling. The injection sites marked in black indicate that these cases contained Ch4 labelling.

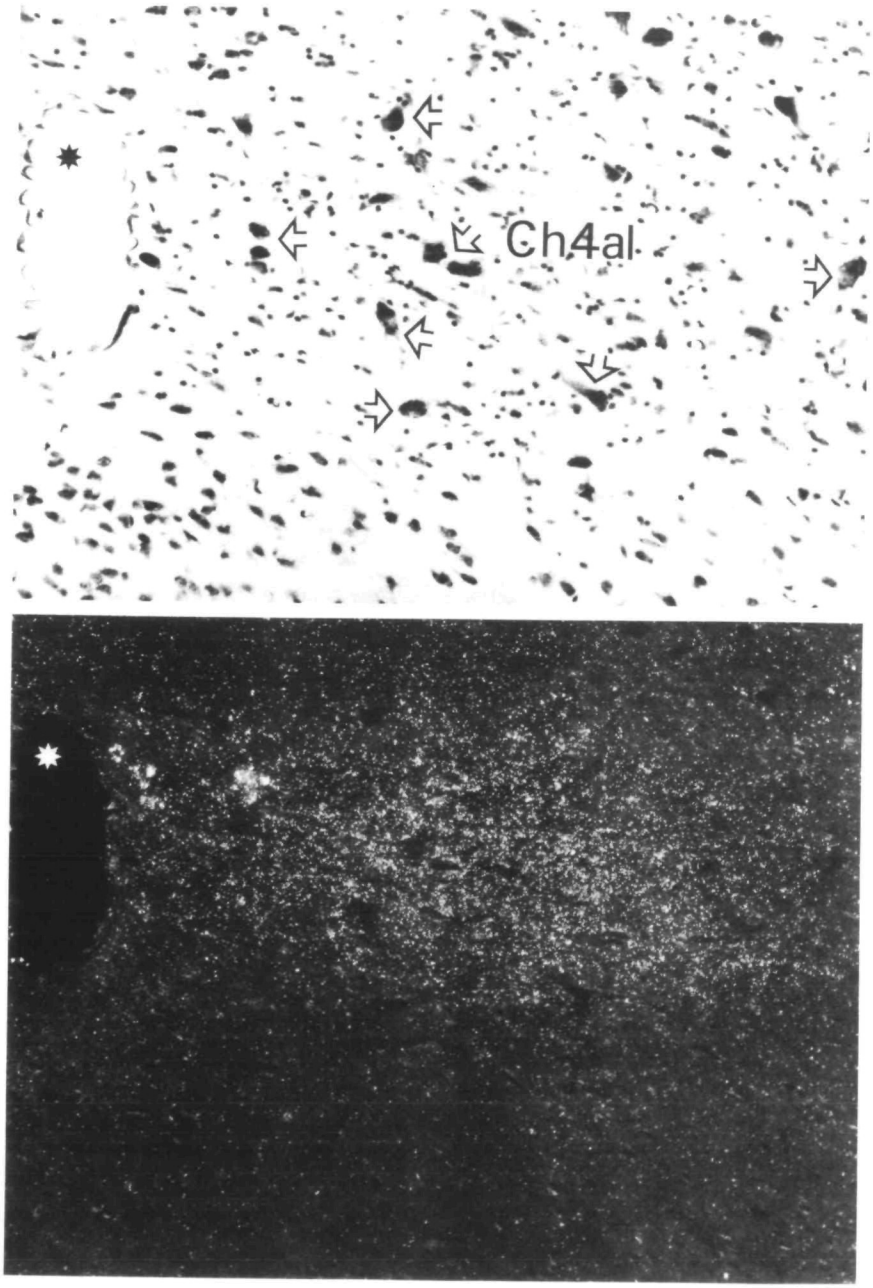

FIG. 4. Photomicrographs from Case 9 which had a caudal orbitofrontal TAA injection site. The upper photomicrograph was taken with bright-field illumination. It shows the part of Ch4al which overlies the most caudal portion of the olfactory tubercle. Open arrowheads point to some examples of the large hyperchromic Ch4 neurons. The smaller neurons at the bottom belong to the olfactory tubercle. The lower photomicrograph shows the same area but under dark-field illumination. This makes the silver label stand out as white dots. The label is clearly concentrated in Ch4al and forms dense homogeneous clusters. Since there are no linear streaks of silver grains, this label represents axonal terminals rather than passing fibres. For purposes of orientation the arteriole in both photomicrographs has been marked with an asterisk. ×266.

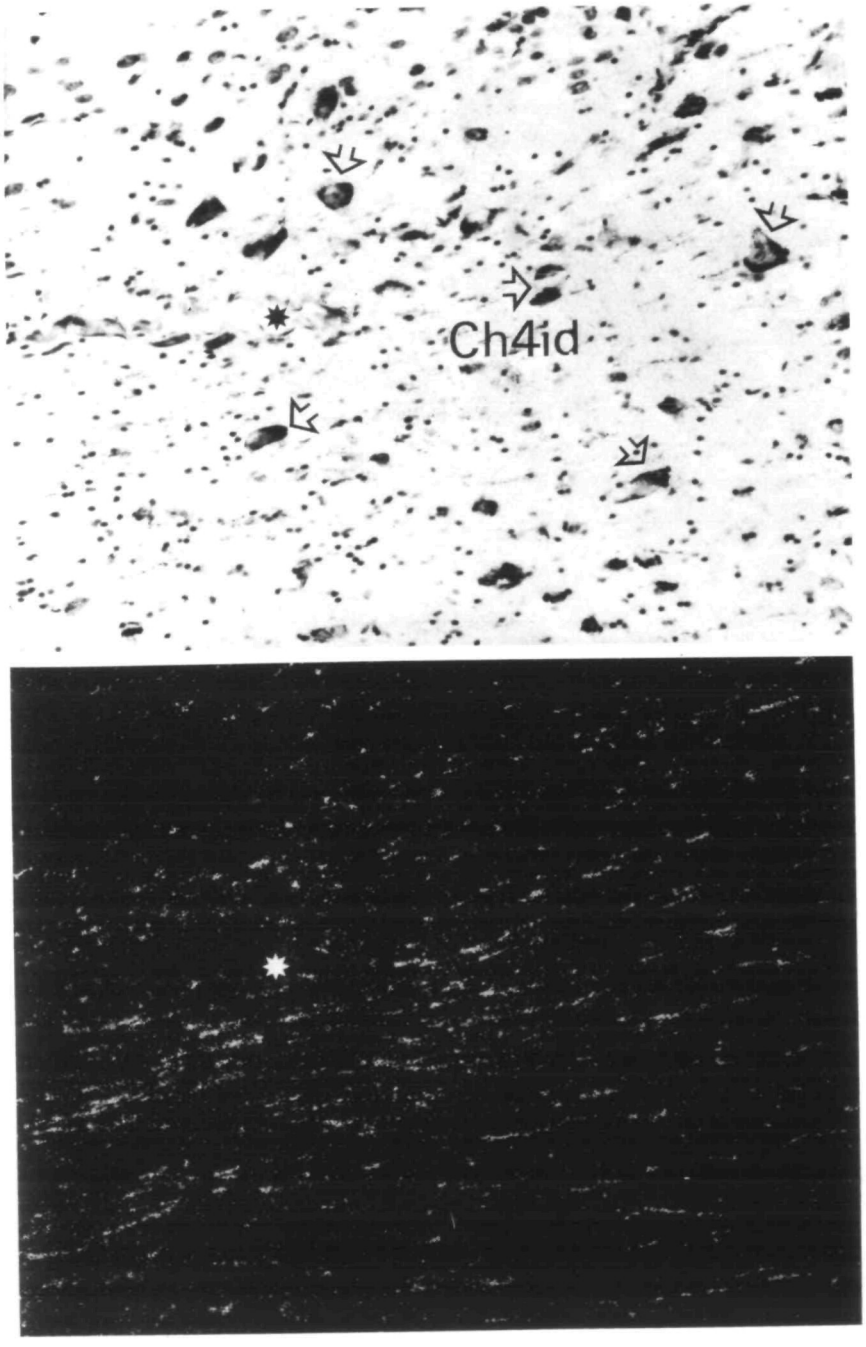

FIG. 5. Photomicrographs from Ch4id of Case 18 which had a TAA injection site in the midcaudal parahippocampal gyrus. The upper photomicrograph was taken with bright-field illumination. Open arrowheads point to some examples of Ch4 neurons. The lower photomicrograph shows the same area but under dark-field illumination. This makes the silver label stand out as white dots. The great majority of the label forms linear streaks and is undoubtedly within passing fibres. This was the only type of label seen in the Ch4 of this case which was therefore considered negative. In the vast majority of the other negative cases even this linear labelling was absent from Ch4. For purposes of orientation the arteriole in both photomicrographs has been marked with an asterisk. ×266.

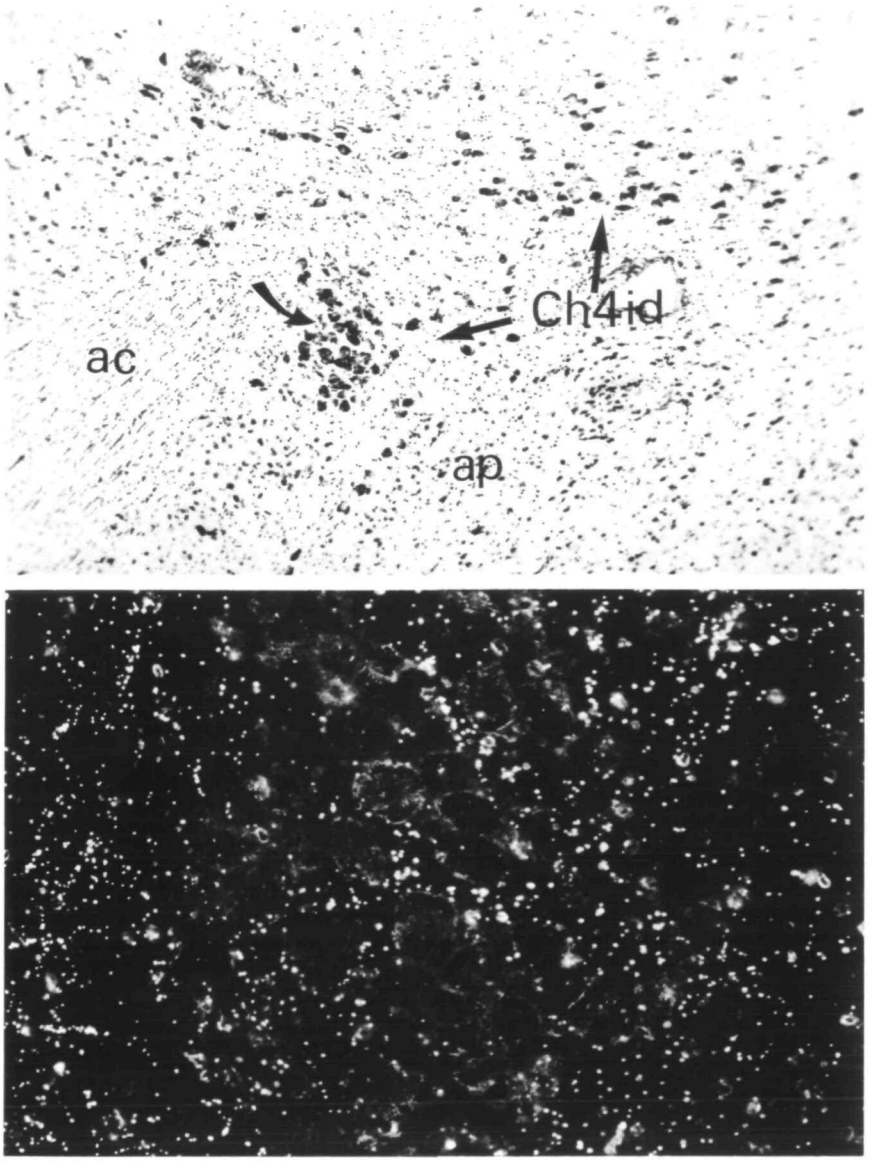

FIG. 6. Photomicrographs from Case 21 which had an entorhinal TAA injection site. *Upper*, bright-field illumination shows two islands of Ch4id (straight arrows). The curved arrow points to the neurons that have been magnified in the lower photomicrograph. × 70. *Lower*, dark-field illumination shows the silver grain label as white dots. This label surrounds the Ch4id perikarya indicated by the curved arrow in the upper photomicrograph. × 500.

TABLE. DISTRIBUTION OF ANTEROGRADE LABELLING WITHIN SECTORS OF Ch4

Case No.	TAA injection site	Distribution of anterograde labelling: Ch4am	Ch4al	Ch4id	Ch4iv	Ch4p
1.	Dorsolateral prefrontal (areas 46 and 10)	–	–	–	–	–
2.	Dorsolateral prefrontal (area 8)	–	–	–	–	–
3.	Dorsolateral prefrontal (areas 45-46)	–	–	–	–	–
4.	Frontal operculum (area 6)	–	–	–	–	–
5.	Frontal operculum (area 6)	–	–	–	–	–
6.	Prefrontal-orbitofrontal (area 12)	–	+	+ + +	+	–
7.	Prefrontal-orbitofrontal (area 12)	+	+	+	+ +	–
8.	Orbitofrontal (area 13)	+	+ + + +	+ + + +	+ + + +	–
9.	Orbitofrontal (area 13)	–	+ + +	+	+ + +	–
10.	Somatosensory (area 2)	–	–	–	–	–
11.	Somatosensory association (area 5)	–	–	–	–	–
12.	Inferior parietal lobule (area 7)	–	–	–	–	–
13.	Medial parietal (areas 5-7)	–	–	–	–	–
14.	Peristriate (areas 18-19)	–	–	–	–	–
15.	Auditory association (area 22 or TA)	–	–	–	–	–
16.	Auditory association (area 22 or TA)	–	–	–	–	–
17.	Visual association (area TE)	–	–	–	–	–
18.	Parahippocampal gyrus (area TF-TH)	–	–	–	–	–
19.	Parahippocampal gyrus (area TF)	–	?+	?+	?+	–
20.	Medial visual association (area TEm + perirhinal cortex)	–	+ +	+ + +	+ + +	–
21.	Entorhinal area	–	+ +	+ + +	+ +	–
22.	Hippocampus	–	–	–	–	–
23.	Temporopolar and superior temporal (areas TG-TA)	–	–	+	+	+ + + +
24.	Temporopolar and superior temporal (areas TG-TA)	–	+	+ + +	+ + +	+ + + +
25.	Prepyriform olfactory cortex and endopiriform nucleus	+	+ +	+ + +	+ + +	–
26.	Posterior insula	–	–	–	–	–
27.	Middle insula	–	–	–	–	–
28.	Anterior insula	–	+ +	+ + +	+ + +	+
29.	Anterior cingulate (area 25)	–	–	–	–	–
30.	Anterior cingulate (area 24)	?+	?+	?+	?+	–
31.	Middle cingulate (areas 24-23)	–	–	–	–	–
32.	Posterior cingulate (area 23)	–	–	–	–	–
33.	Retrosplenial area	–	–	–	–	–
34.	Lateral septum	+ + + +	+ + + +	+ + + +	+ + + +	+
35.	Medial septum	+ + +	+ + +	+ + +	+ +	–
36.	Nucleus accumbens-ventral pallidum	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
37.	Medial hypothalamus	+ +	+ +	+ + +	+ + +	+ + +

The location of the TAA injection site in each case is shown in figs. 2 and 3. In describing the injection site, we used the nomenclature of Walker (1940) for areas 10, 12, 13, 23-25, 45, 46, the nomenclature of Brodmann (1905) for areas 2, 5-7, 18, 19, 22, the nomenclature of Bonin and Bailey (1947) for areas TE, TF, TH, TA, TG and the nomenclature of Turner *et al.* (1980) for area TEM. The negative (–) sign indicates that the terminal field labelling was not above the background level. The plus (+) signs indicate that this type of labelling was above background, + + + + showing the highest level of labelling. The question marks indicate that the presence of labelling could not be established with certainty.

The injection site in Cases 23 and 24 was located within the most anterior and temporopolar part of the superior temporal gyrus, at the junction between areas TA and TG of Bonin and Bailey (fig. 2). Both cases contained intense Ch4 labelling, mostly within the Ch4p sector (Table). In Case 25, the TAA injection site was mostly within the temporal limb of prepyriform olfactory cortex with a minor extension into the underlying endopyriform nucleus (fig. 3). This case contained intense Ch4 labelling, especially in Ch4i.

Insular TAA Injections

In Cases 26 to 28, the injection sites were located within insular cortex, with minor extension into the underlying claustrum (fig. 2). Cases 26 and 27, in which the injection sites were confined to the posterior and middle insula, did not contain terminal labelling in Ch4. Case 28 with a TAA injection in the anterior insula, contained Ch4 labelling in a terminal field pattern, especially in the Ch4i sector (Table).

Cingulate TAA Injections

In Cases 29 to 33, the injection site was located within the cingulate and retrosplenial areas (fig. 2). With the possible exception of Case 30 in the anterior cingulate cortex, none of these cases contained Ch4 labelling within terminal fields.

Subcortical TAA Injections

In Case 34, the injection site was centred within the lateral septal area and in Case 35 within the medial septum and adjacent vertical diagonal band nucleus (fig. 3). Both these cases had intense terminal field labelling within Ch4 which extended to most sectors except Ch4p (Table). In Case 36, the injection site was mostly within the medial portion of the nucleus accumbens but probably also extended into the adjacent ventral pallidum (fig. 3). This case contained intense terminal labelling in virtually all Ch4 sectors (Table). The injection in Case 36 was confined to the medial hypothalamic region and also yielded widespread Ch4 labelling in a terminal field pattern (Table).

The Interpretation of Anterograde Labelling

Two limitations of the autoradiographic method are pertinent to this study. First, very low levels of anterograde transport are extremely difficult to differentiate from background grain. We cannot therefore entirely rule out the possibility that some of the cases which we classified as negative could have contained sparse labelling within Ch4. We used relatively long autoradiographic exposure times in order to decrease the likelihood of such false negative outcomes. Secondly, light microscopic autoradiography often raises the question of whether the label is within terminal fields where synaptic contact occurs or merely in axons on their way to other regions of the brain. This consideration is particularly germane to this study since one property of the Ch4 complex is its intimate association with the many fibre tracks which traverse

the basal forebrain. These fibre bundles include the medial forebrain bundle, the ansa peduncularis, the inferior thalamic peduncle, the ansa lenticularis, the medullary laminae of the globus pallidus, the anterior commissure and the internal capsule (Mesulam *et al.*, 1983*a*). In each of the positive cases, one or more of these pathways contained labelled fibres on their way to the striatum, the thalamus, the amygdala, the brainstem and the opposite hemisphere. However, many of the negative cases also contained label in these pathways. Labelled fibres usually yield a distinctive linear streak of silver grain, especially when they run parallel to the plane of section, whereas labelled terminal zones have a more homogeneous distribution of label, especially around perikarya. In all our positive cases, this latter type of distribution was present. However, the possibility that even some of this labelling could be attributed to passing fibres rather than to terminals cannot be ruled out entirely. A complementary way of determining afferent projections is to administer retrogradely transported tracers into the region of interest. This is not practical, however, in this case since Ch4 is embedded within many fibre bundles and since currently available retrograde tracers are readily taken up and transported by passing fibres. A more definitive resolution of this matter will therefore require additional electrophysiological and ultrastructural investigations.

Course of Labelled Fibres

The labelled fibres from orbitofrontal regions (Cases 6 to 9) and from the anterior insula (Case 28) coursed in the external and extreme capsules before entering the region containing Ch4. Fibres from medial (Cases 20, 21) and polar (Cases 23, 24) temporal cortex travelled in a position lateral to the amygdala within the uncinate fasciculus and then curved medially towards the Ch4 complex. The septal projections to Ch4 (Cases 34, 35) coursed mostly within the diagonal band of Broca. The labelled axons from the accumbens-ventral pallidum (Case 36), from the prepyriform cortex (Case 25) and from the hypothalamus (Case 37) were widely distributed within the basal forebrain.

DISCUSSION

The Ch4 complex (nucleus basalis-substantis innominata-nucleus of the ansa peduncularis) occupies a pivotal position in the transmitter circuitry of the brain since it provides the great majority of the cholinergic innervation for the entire neocortical mantle (Mesulam *et al.*, 1983*a*). A large number of complex cognitive and affective behaviours, ranging from memory to aggression, are markedly influenced by pharmacological agents which alter central cholinergic transmission (Drachman and Leavitt, 1974; Butcher and Woolfe, 1982). It is therefore quite likely that the Ch4 complex participates in the modulation of these behaviours.

Pathological alterations in the Ch4 complex have been reported in several neuropsychiatric disease entities. In Huntington's disease and also in schizophrenia, neurons in various stages of degeneration, a decrease of neuronal volume and

fibrillary gliosis have been noted in the Ch4 region even though consensus on the universality of these changes is still awaited (Buttlar-Brentano, 1952; Averback, 1981; Stevens, 1982). The most striking and consistent alterations in Ch4 have been observed in Alzheimer's disease and in Parkinson's disease. Ishii (1966) described extensive neurofibrillary degeneration in the Ch4 region (substantia innominata) of patients with Alzheimer's disease. Pilleri (1966) also described massive neuronal loss in Ch4 (nucleus of Meynert) in a patient with Alzheimer's disease and attributed this to retrograde degeneration secondary to atrophy in temporal cortex. The considerable cell loss in the Ch4 complex (nucleus basalis) in Alzheimer's disease has since been documented with greater certainty (Whitehouse *et al.*, 1981; Tagliavini and Pilleri, 1983). The reported loss of choline acetyltransferase activity in the Ch4 region (substantia innominata) of patients with Alzheimer's disease lends further support to these observations (Rossor *et al.*, 1982). Since Ch4 is the major source of cortical cholinergic innervation, loss of neurons in this complex would be expected to result in a decrease of presynaptic cholinergic markers without necessarily leading to a change in the postsynaptic cholinergic receptor density. This is precisely what has been reported in numerous investigations which have found diminished choline acetyltransferase activity and normal muscarinic receptor densities in cortical tissue obtained from patients suffering from Alzheimer's disease (Bowen *et al.*, 1976; Davies and Maloney, 1976; *see* Bartus *et al.*, 1982, for review). These observations suggest that the cell loss in Ch4 and the depression of cortical cholinergic innervation may be closely related to each other in Alzheimer's disease even though the direction of causality has not yet been determined with certainty. In at least one test of memory function, the level of performance in patients with Alzheimer's disease was found to correlate inversely with the cortical choline acetyltransferase activity (Fuld, 1982). Since the Ch4 complex is the major source of neocortical cholinergic innervation these observations give further credence to the suggestion that changes in the corticopetal projections from the Ch4 complex may account for some of the mental changes in Alzheimer's disease.

The basal forebrain may not be the *only* source of cortical cholinergic innervation. An intrinsic component may be provided by the choline acetyltransferase containing cortical neurons which have recently been identified in the rodent brain (Houser *et al.*, 1983). When compared to the input from Ch4, these provide a distinctly minor component of the cortical cholinergic innervation (Wenk *et al.*, 1980; Johnston *et al.*, 1981). Nevertheless, if such neurons also exist in the primate, their contribution to the overall pattern of cortical cholinergic innervation and to its behavioural correlates will need to be investigated in the normal brain as well as in the pertinent disease conditions.

Lewy (1913) and Foix and Nicolesco (1925) reported the presence of degenerative changes in the Ch4 region (basal nucleus) in patients with Parkinson's disease. Subsequently, marked neuronal loss in the Ch4 complex has been observed in the parkinsonism-dementia complex of Guam (Nakano and Hirano, 1983) and in parkinsonian patients who also show a picture of dementia (Whitehouse *et al.*,

1983). As in the case of Alzheimer's disease, and in keeping with the consequences of cell loss in Ch4, a decrease in presynaptic cholinergic markers has also been reported in patients with Parkinson's disease (Ruberg *et al.*, 1982). Although Alzheimer's disease and Parkinson's disease have vast differences in their clinical symptomatologies and their overall neuropathological pictures, it is conceivable that the involvement of the corticopetal cholinergic pathway provides a common denominator for some of the cognitive alterations that occur in both of these degenerative disorders.

When the widespread projections from Ch4 to the cortex and the amygdala are considered, it is unlikely that any single behaviour will emerge as the only behavioural specialization of the Ch4 complex. Instead, it is far more likely that there are multiple behavioural correlations, each reflecting the specializations of the cortical targets that receive cholinergic fibres from the Ch4 complex. For example, the cholinergic projections from Ch4 to paralimbic cortex and to the amygdala may be related mostly to memory and affective behaviour, whereas the pathway from Ch4 to association cortex may also subserve other cognitive functions ranging from language to complex perceptual skills. Whether these behavioural relationships are based on a nonspecific arousing effect of cholinergic innervation or if more specific mechanisms are also involved remains to be seen. Neuronal loss in Ch4 may thus account for widespread mental alterations and may participate in some of the neuropsychiatric changes in Huntington's disease, schizophrenia, Alzheimer's disease and Parkinson's disease. Of all these potential neuropathological relationships, the one between Ch4 and Alzheimer's disease may turn out to have the most biological significance, since the decrease of cortical choline acetyltransferase is profound in this disease and since memory function, which appears to depend on the integrity of central cholinergic pathways, is almost always impaired and usually becomes one of the most important limitations in the mental state of these patients.

In view of these potential pathophysiological relationships, it becomes quite desirable to have a clearer understanding of the neural connections of the basalis-substantia innominata-ansa peduncularis complex (Ch4). Previous experiments in the monkey brain had shown that the Ch4 complex projects to all parts of the cortical mantle (Divac, 1975; Kievit and Kuypers, 1975; Mesulam and Van Hoesen, 1976; Mesulam *et al.*, 1977, 1983*a*, *b*; Pearson *et al.*, 1983*b*). In order to have a better appreciation for the type of neural information that the Ch4 complex conveys to the neocortex, it is also necessary to understand the neural input that Ch4 receives. Our observations in the experiments described above lead to the rather unexpected conclusion that the great majority of the Ch4 connections with the neocortex are not reciprocal. For example, vast portions of dorsolateral frontal cortex, posterior parietal cortex, peristriate cortex, lateral temporal cortex, posterior insula and cingulate cortex do not seem to send projections to the Ch4 complex even though each one of these areas receives inputs from Ch4. The cortical projections into Ch4 arise from the orbitofrontal regions, the temporal pole, the prepyriform cortex, the

entorhinal cortex, the medial inferotemporal cortex and the anterior insula. Additional subcortical projections originate in the medial hypothalamus, the septal nuclei and the region of the nucleus accumbens-ventral pallidum. Although we did not have cases with TAA injections within the amygdala, projections from amygdaloid nuclei to the Ch4 complex have been reported by others (Price and Amaral, 1981). The one common characteristic of nearly all these cortical and subcortical projections to the Ch4 complex is that they originate in limbic and paralimbic portions of the brain. This connectivity pattern has important implications for the feedback regulation of cortical cholinergic transmission. The few cortical areas which do have direct projections into Ch4 can potentially influence not only the level of cholinergic signals that they receive but also the cholinergic innervation to other parts of the cortex. Perhaps this is one reason why many of the regions which project to Ch4 are also of crucial importance to memory function. On the other hand, the vast majority of the cortical surface including most of the sensorimotor areas and high-order association cortices have no direct feedback control over the cholinergic input they receive from Ch4. The physiological implications of this arrangement remains to be elucidated. It is reasonable to expect that retrograde cellular changes in Ch4 would be most conspicuous after lesions that involve those cortical areas that do have reciprocal connections with Ch4 since this would damage not only the axons of Ch4 neurons but also the terminals they receive. This may well be the basis of several earlier reports which detected retrograde degeneration in Ch4 following relatively limited temporal lobe damage but not after comparable damage elsewhere in the cortex (Kodama, 1929; Gorry, 1963; Pilleri, 1966). More recently, retrograde cell degeneration in Ch4 has been reported after frontal and parietal lobe lesions as well, but only in cases which contained very extensive cortical damage (Pearson *et al.*, 1983*a*).

Despite considerable overlap, a certain topographical arrangement can be detected in the connectivity from subsectors of the Ch4 complex into neocortex (Mesulam *et al.*, 1977; 1983*a*, *b*). The anteromedial sector (Ch4am) is the major source of Ch4 projections to cortical areas along the medial wall of the hemispheres, the anterolateral sector (Ch4al) to parietofrontal opercular areas, and the intermediate sector (Ch4i) to a variety of dorsolateral frontoparietal, orbitofrontal, insular, peristriate and inferotemporal areas. The posterior sector (Ch4p) is the major source of projections to superior temporal and adjacent temporopolar cortex. The cortical areas that do have reciprocal projections back into Ch4 appear to respect this topography. For example, the input from the anterior insula, the inferior temporal and the orbitofrontal cortex was most concentrated in Ch4i which is also the major source of reciprocal projections to the same cortical areas. The input from superior temporopolar areas, on the other hand, was concentrated mostly in Ch4p, the same sector which is the major source of the reciprocal Ch4 projection into superior temporal-temporopolar regions.

The limbic and paralimbic cortex can be divided into two large classes. On the one hand, the hippocampal and induseal allocortex provide a focus for the paralimbic

cortex of the parahippocampal, cingulate and subcallosal regions. On the other hand, the prepyriform allocortex provides a focus for the paralimbic formations of the orbitofrontal, insular and temporopolar regions (Mesulam and Mufson, 1982*a*). It appears that Ch4 is preferentially under the influence of this second set of limbic-paralimbic areas. The behavioural specializations of the insulo-orbitotemporal component of the paralimbic brain are related to autonomic function, feeding behaviour, olfactogustatory sensation, interspecies affiliative behaviour, motivation and some aspects of learning and memory (Mesulam and Mufson, 1982*a*). It is conceivable that the behavioural relationships of Ch4 will also reflect the same set of specializations. Direct connections have been demonstrated from what appears to be the equivalent of Ch4 in the rabbit to the nucleus of the tractus solitarius (Schwaber *et al.*, 1982). Such a projection would allow the Ch4 complex to have a profound influence on the regulation of autonomic function. The heavy projections from the septal nuclei, from the hypothalamus and from the amygdala, are consistent with these behavioural affiliations and also suggest that the Ch4 neurons may be particularly sensitive to the internal milieu. The ventral pallidum and the nucleus accumbens are thought to constitute a limbic component of the extrapyramidal system (Heimer and Wilson, 1975). It is interesting that these regions also project into Ch4. In awake and behaving macaque monkeys, Ch4 (substantia innominata) neurons responded to the delivery of a juice reward and also to the sight and taste of food in a manner which reflected the food preferences and state of hunger of the individual animal (DeLong, 1971; Burton *et al.*, 1975; Rolls *et al.*, 1979). These observations are also consistent with the suggestion that Ch4 neurons are particularly responsive to motivation states. The Ch4 neurons are therefore in a position to act as a cholinergic relay for influencing the activity of the entire neocortex according to the prevailing motivational state.

The responsivity of Ch4 neurons to the sight and taste of food implies that they must be receiving complex sensory information in several modalites. The projections that we have demonstrated indicate several potential routes for this sensory input. The olfactory information appears to have the most direct access to the Ch4 complex from primary olfactory cortex in the prepyriform region. Gustatory, visceral and perhaps also somaesthetic inputs might be relayed through the projections from the anterior insula into Ch4 (Mesulam and Mufson, 1982*b*). Auditory input could reach Ch4 from the anterior portions of the superior temporal region. The projection from the medial inferotemporal region (TEm) to Ch4 could carry information about the visual environment. Additional sensory information to Ch4 could be relayed by the amygdala. These observations show that the Ch4 complex has potential access to all sensory modalities. Except for the olfactory modality, sensory information from cortex reaches Ch4 only after extensive cortical preprocessing since the Ch4 complex does not appear to receive direct input from primary sensory or parasensory regions of the brain in the visual, auditory and somaesthetic modalities.

Cholinergic transmission in the central nervous system has a very ancient origin

and can be identified in the brains of reptiles (Desan *et al.*, 1983; Höhmann *et al.*, 1983). The Ch4 complex, however, does not represent a vestigial structure with respect to phylogenetic development. There is a dramatic increase in the prominence of the Ch4 complex in the course of evolution in a manner which seems to reflect the development of the neocortical mantle (Gorry, 1963; Parent *et al.*, 1979; Mesulam *et al.*, 1983*c*). This nuclear complex is quite rudimentary and only incompletely demarcated from the adjacent globus pallidus in rodents, insectivores and carnivores (Gorry, 1963). In cetacea and in primates—especially in man—the Ch4 complex shows a vast increase in size and in differentiation from adjacent nuclear formations. It is therefore not surprising to find that this nuclear formation may be related to complex behaviour and that it may play a role in the alterations in mental state which emerge in the course of several neuropsychiatric disease conditions.

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