

# Laminar and Regional Distributions of Neurofibrillary Tangles and Neuritic Plaques in Alzheimer's Disease: A Quantitative Study of Visual and Auditory Cortices

David A. Lewis,<sup>1,a</sup> Michael J. Campbell,<sup>1</sup> Robert D. Terry,<sup>2</sup> and John H. Morrison<sup>1</sup>

<sup>1</sup>Department of Basic and Clinical Research, Scripps Clinic and Research Foundation, La Jolla, and <sup>2</sup>Departments of Neurosciences and Pathology, University of California, San Diego, La Jolla, California

**The number of Thioflavine S-positive neurofibrillary tangles (NFT) and neuritic plaques (NP) was determined in visual and auditory cortical regions of 8 patients with Alzheimer's disease. On both a regional and laminar basis, NFT exhibited very distinctive and consistent distribution patterns. The mean ( $\pm$ SEM) number of NFT in a 250- $\mu$ m-wide cortical traverse was very low in area 17, primary visual cortex ( $0.9 \pm 1.0$ ), increased 20-fold in the immediately adjacent visual association cortex of area 18 ( $19.7 \pm 3.6$ ), and showed a further doubling in area 20, the higher-order visual association cortex of the inferior temporal gyrus ( $35.5 \pm 8.8$ ). Similar differences in NFT number were present between primary auditory ( $1.6 \pm 0.5$ ) and auditory association ( $18.9 \pm 5.4$ ) regions. On a laminar basis, NFT were predominantly present in layers III and V, although there were striking regional differences in the proportion of NFT in these 2 layers. Layer III contained 79% of the NFT in layers III and V in area 18, 41% in area 20, and only 27% in area 22.**

**In contrast, NP showed different, and less specific, regional and laminar distribution patterns. Total NP number was similar in the 3 visual areas, although there were marked regional differences in the type of NP present. Nearly 80% of the NP in area 17 was of the NPc type (i.e., contained a dense, brightly fluorescent core), whereas over 70% of the NP in both areas 18 and 21 was of the NPnc type (i.e., lacked a dense, brightly fluorescent core). NP were present in every cortical layer but were most numerous in layers III and IV.**

**The distinctive distribution patterns of NFT are very similar to the regional and laminar locations of long corticocortical projection neurons in homologous regions of monkey neocortex. This association suggests that NFT reside in the cell bodies of a subpopulation of pyramidal neurons, namely, those that furnish long corticocortical projections. In contrast, the distribution patterns of NP suggest that multiple neuronal systems contribute to their formation.**

Neurofibrillary tangles (NFT) and neuritic plaques (NP) are the histological hallmarks of Alzheimer's disease (AD). NFT represent the accumulation of abnormal paired helical filaments in the cytoplasm of neurons, whereas NP are composed of dystrophic neurites and glial processes, with or without an amyloid core (Terry and Wisniewski, 1970). In the cerebral cortex, NFT appear to develop primarily in the cell bodies of pyramidal neurons, and both NFT and NP are thought to be more common in association than in primary sensory or motor regions (for reviews, see Terry and Katzman, 1983; Kemper, 1984; Perry, 1986). However, the precise elements of cortical circuitry compromised by these pathological changes have remained obscure.

Over the past 20 years, improvements in neuroanatomical techniques, especially tract-tracing and immunohistochemical methods, have allowed for the detailed study of the organization of neocortical circuitry in primate brain. Such studies have helped define the regional and laminar locations of the origins and terminations of cortical efferents and afferents, respectively. These distribution patterns have been extensively characterized in visual cortical regions (for reviews, see Tigges and Tigges, 1985; Valverde, 1985; Van Essen, 1985) and have also been examined in auditory cortical regions (Galaburda and Pandya, 1983; Pandya and Yeterian, 1985).

In order to determine what elements of cortical circuitry might be involved in the pathological changes of AD, we quantified the regional and laminar distributions of both NFT and NP in visual and auditory cortices from brains of patients with AD. The regional and laminar distributions of NFT were strikingly similar to the known distribution of pyramidal neurons that furnish long corticocortical projections in homologous regions of monkey cortex, indicating that NFT may reside in the cell bodies of that subclass of pyramidal neurons that furnish long corticocortical projections in human neocortex. In contrast, NP had different and less specific regional and laminar distributions than did NFT, a finding consistent with other observations that suggested that multiple neuronal systems contribute to NP formation.

## Materials and Methods

Brains from 8 patients (age range, 48-82 years) with a clinical diagnosis of AD were analyzed in this study. The clinical diagnosis in each case was confirmed by neuropathological evaluations that demonstrated atrophy and the presence of both NFT and NP in multiple regions of the neocortex and hippocampus.

Brains were removed and placed in either 4% paraformaldehyde or 10% formalin for 3-10 d. Coronal blocks of tissue were taken from 3 cortical locations: the medial occipital lobe 2.0-3.0 cm rostral to the

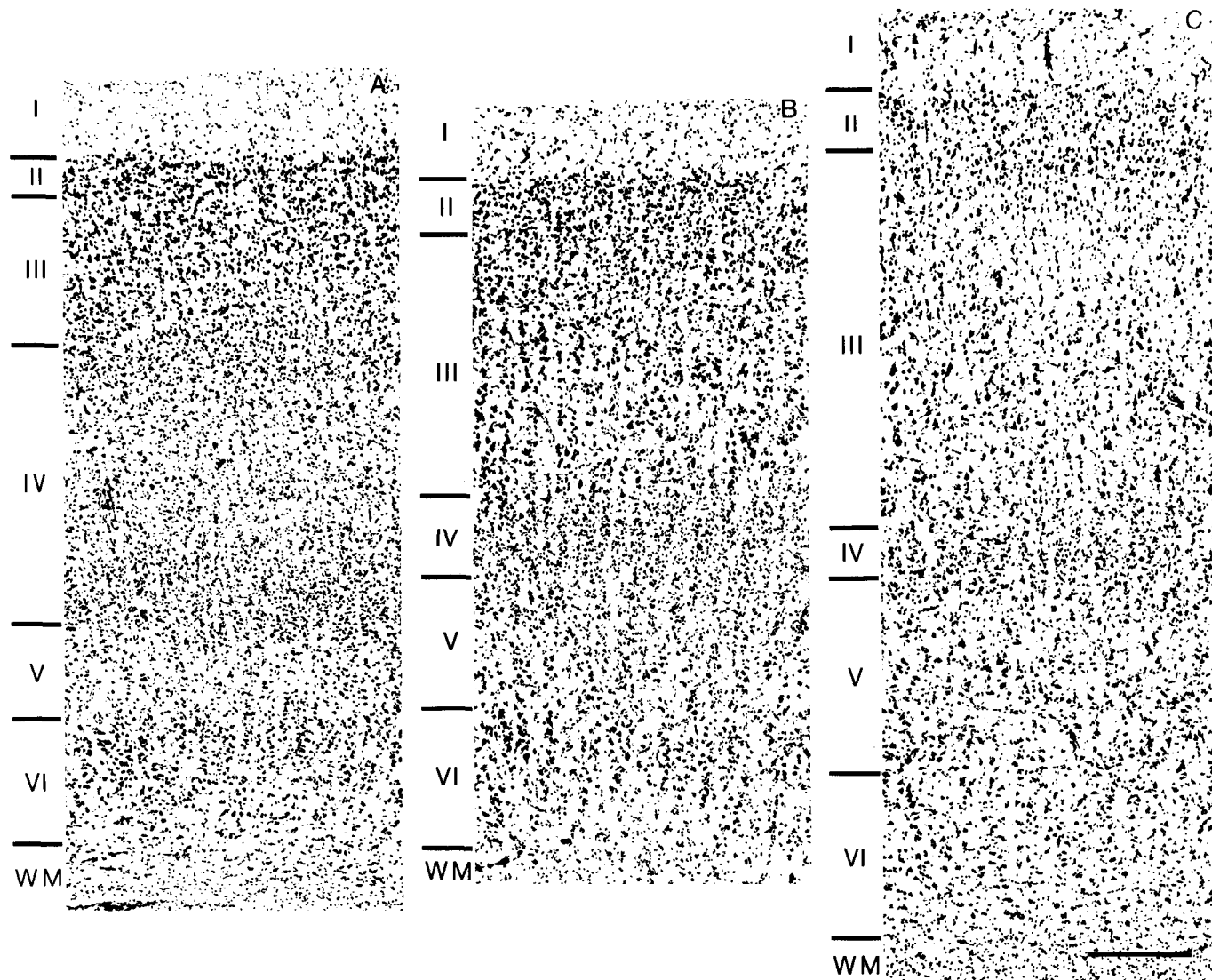
Received Aug. 12, 1986; revised Dec. 9, 1986; accepted Dec. 23, 1986.

We thank F. E. Bloom for consultation during the course of these studies, J. Polich for advice on the statistical analyses, and G. Huntley and D. Benson for excellent technical assistance. This work was supported by NIMH Research Scientist Development Award MH-00519, NIAAA Grant AA-07456, NIA Grants AG-05131 and AG-05386, the Alzheimer's Disease and Related Disorders Association, the MacArthur Foundation, and the McKnight Foundation.

Correspondence should be addressed to John H. Morrison, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla, CA 92037.

<sup>a</sup> During the course of this work, D.A.L. was on a leave of absence from the Departments of Psychiatry and Internal Medicine, University of Iowa, Iowa City, IA.

Copyright © 1987 Society for Neuroscience 0270-6474/87/061799-10\$02.00/0



**Figure 1.** Cresyl violet-stained sections of Brodmann's areas 17 (*A*), 18 (*B*), and 20 (*C*) from the brain of a patient with AD. Roman numerals indicate the cortical layers. Despite the cortical pathology present in AD, note that the cytoarchitectonic characteristics and laminar boundaries of these regions are still clearly discernible. Calibration bar, 300  $\mu\text{m}$  (*A-C*).

occipital pole; the inferior temporal gyrus at the level of the lateral geniculate nucleus; and Heschel's gyri and the adjacent lateral surface of the superior temporal gyrus. Tissue blocks were then washed in a series of cold, graded sucrose solutions and sectioned coronally in a cryostat at 40  $\mu\text{m}$ . Sections were mounted on gelatin-coated slides and air-dried. They were then defatted in xylene, rehydrated, stained with 1% aqueous Thioflavine S (Schwartz, 1972), dehydrated in a series of alcohols, and coverslipped with Permount. Thioflavine S is a fluorescent stain that visualizes both extracellular amyloid and intracellular paired helical filaments. Thus, in Thioflavine S-stained material, NFT are evident as fluorescent material in the perinuclear cytoplasm and proximal processes of neurons (Fig. 2), whereas NP appear as the accumulation of fluorescent fibrous material, with or without a dense, brightly fluorescent core (Fig. 5). Although some quenching of the fluorescence occurs, stained structures remain clearly visible even after prolonged exposures under the fluorescent microscope. Other sections were stained with cresyl violet.

Cytoarchitectonic regions (Fig. 1) were identified according to published criteria (Brodmann, 1909; Bailey and Von Bonin, 1951). The following Brodmann's areas were studied: the portion of area 17 (primary visual cortex) located within the calcarine sulcus; area 18, the visual association cortex located immediately adjacent to area 17; area 20, the higher-order visual association cortex of the inferior temporal

gyrus; area 41, the cytoarchitectonically distinct primary auditory region of Heschel's gyri; and the portion of area 22 (auditory association cortex) located immediately lateral to Heschel's gyri in the superior temporal gyrus.

Sections stained with Thioflavine S were examined under a computer-assisted Zeiss inverted microscope (Young et al., 1985) using the Zeiss filter pack 487702 (excitation wavelength, 365–395 nm). For each cortical region, NFT were counted in a 250- $\mu\text{m}$ -wide cortical traverse from 10 sections (80–120  $\mu\text{m}$  apart) per brain at a magnification of 250 $\times$ . NP in the 3 visual areas were counted in a 500- $\mu\text{m}$ -wide cortical traverse from 8 sections (80–120  $\mu\text{m}$  apart) per brain at a magnification of 100 $\times$ . NP were divided into 2 categories based upon their morphological appearance (Fig. 5): NP containing any degree of a dense, brightly fluorescent core (neuritic plaque, with core—NPc) were distinguished from those lacking this appearance (neuritic plaque, no core—NPnc). The laminar distributions of NFT and NP were determined by comparing the distance from the pial surface of each NFT and NP in a Thioflavine S-stained section with the distance from the pial surface of the laminar boundaries on an adjacent Nissl-stained section.

Differences in the number of NFT and NP among cortical areas, or across cortical layers within areas, were compared with 2-factor (area  $\times$  case or layer  $\times$  case), repeated-measures (section) analyses of variance. Tukey's method ( $\alpha$  level = 0.05) was used for between-group compar-

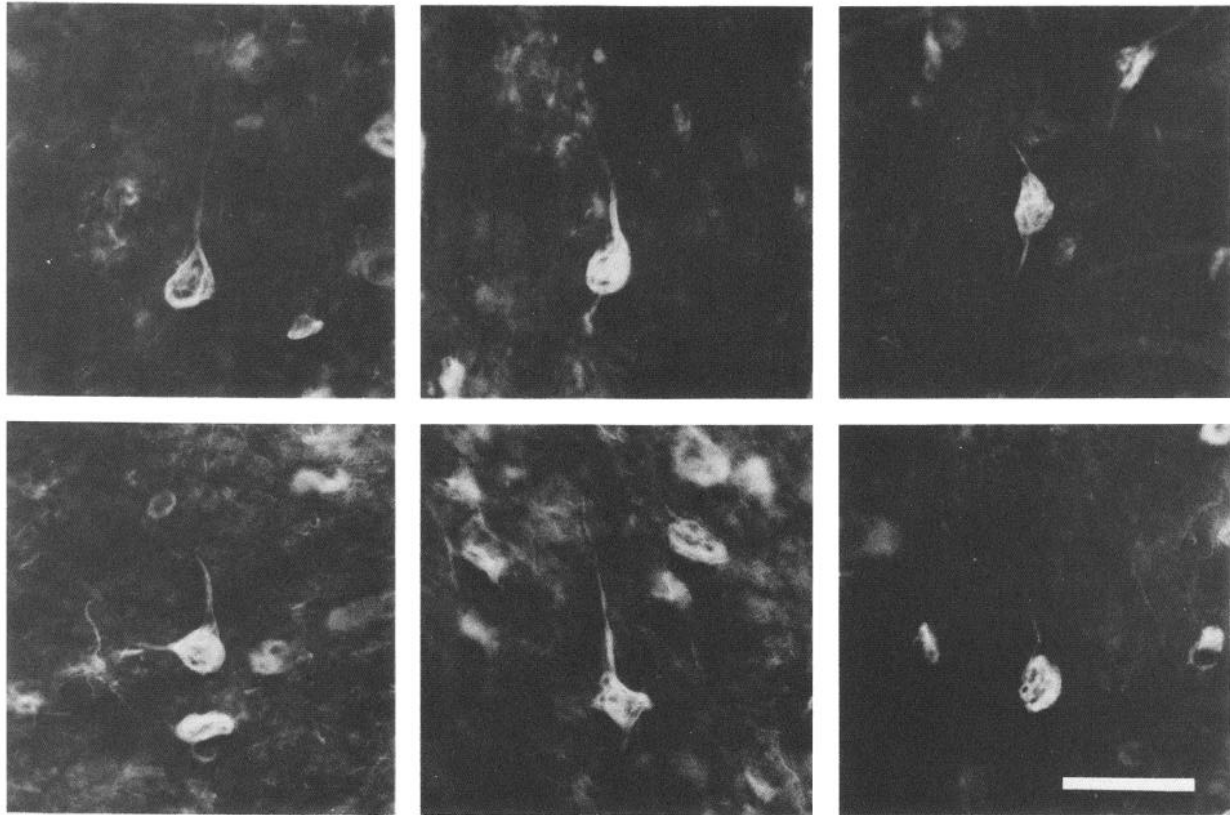


Figure 2. Representative examples of neurofibrillary tangles (NFT) as revealed by Thioflavine S staining. Note that the fluorescent material is present in the cell bodies and apical and/or basilar dendrites of what appear to be pyramidal neurons. Calibration bar, 40  $\mu$ m.

isons (Kleinbaum and Kupper, 1978). Statistical significance of the Pearson correlation coefficients was determined using 1-sample *t* tests (Rosner, 1982).

## Results

### Neurofibrillary tangles

Examples of the morphological appearance of NFT are shown in Figure 2. As far as could be determined with light microscopy, the vast majority, if not all, of the NFT were located in the cell bodies of pyramidal neurons.

The number of NFT present in a 250- $\mu$ m-wide cortical traverse differed markedly among cortical regions. In the 6 cases

Table 1. Distribution of NFT in cortical visual regions of patients with AD

Case	Age (yr)	Cortical region		
		17	18	20
4101	82	0.2 $\pm$ 0.1	9.8 $\pm$ 1.5	7.8 $\pm$ 1.1
4163	74	0.1 $\pm$ 0.1	13.0 $\pm$ 0.7	24.4 $\pm$ 1.6
4037	71	0.1 $\pm$ 0.1	15.0 $\pm$ 1.5	22.1 $\pm$ 1.3
5147	68	0.5 $\pm$ 0.3	19.9 $\pm$ 2.2	57.5 $\pm$ 3.9
1885	63	2.0 $\pm$ 0.6	30.3 $\pm$ 1.6	63.5 $\pm$ 5.2
4114	62	2.4 $\pm$ 0.5	30.4 $\pm$ 2.3	37.5 $\pm$ 2.0
Mean <sup>a</sup>		0.9 $\pm$ 1.0*	19.7 $\pm$ 3.6†	35.5 $\pm$ 8.8‡

Values for each case are the mean ( $\pm$ SEM) number of tangles in a 250- $\mu$ m-wide cortical traverse (*n* = 10 sections).

<sup>a</sup> ANOVA:  $F_{2,10} = 14.19$ ;  $p = 0.0012$ . Values not sharing the same superscript are significantly different ( $p < 0.05$ ).

in which visual areas were examined (Table 1), the mean ( $\pm$ SEM) number of NFT in area 17 (primary visual cortex) was very low ( $0.9 \pm 1.0$ ). In contrast, in the immediately adjacent area 18 (visual association cortex), there was a 20-fold increase in the number of NFT ( $19.7 \pm 3.6$ ). Area 20 (higher-order visual association cortex of the inferior temporal gyrus) was characterized by a further doubling in NFT number ( $35.5 \pm 8.8$ ). These differences among regions were evident in each case, with the exception of number 4101, in which areas 18 and 20 did not differ in NFT number (Table 1).

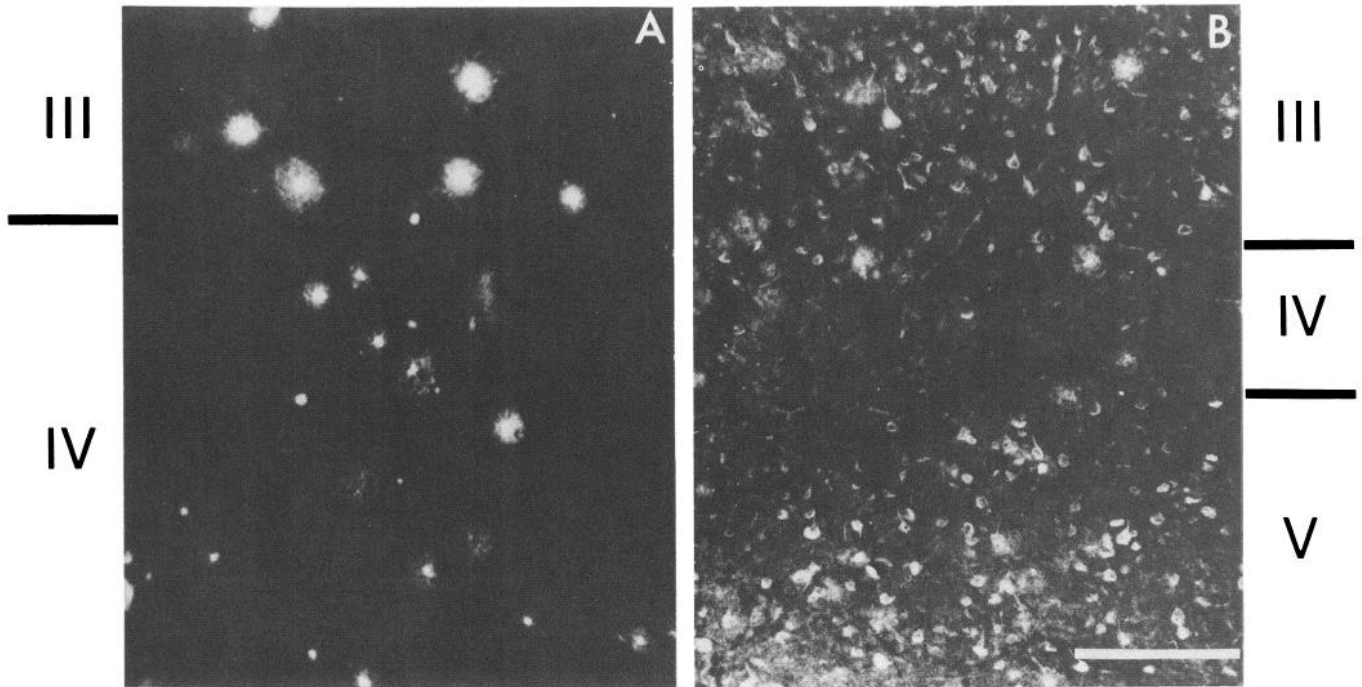
Similar differences in NFT distribution were present between the auditory regions (Table 2). Primary auditory cortex (area 41) had a very low number of NFT ( $1.6 \pm 0.5$ ), whereas area 22 (auditory association cortex) had a greater than 10-fold in-

Table 2. Distribution of NFT in cortical auditory regions of patients with AD

Case	Age (yr)	Cortical region	
		41	22
4101	82	0.3 $\pm$ 0.1	7.6 $\pm$ 1.0
4114	62	1.2 $\pm$ 0.2	10.9 $\pm$ 1.1
4037	71	1.3 $\pm$ 0.4	12.7 $\pm$ 0.8
3385	71	2.0 $\pm$ 0.5	34.9 $\pm$ 1.8
0586	48	3.2 $\pm$ 0.8	28.2 $\pm$ 1.4
Mean <sup>a</sup>		1.6 $\pm$ 0.5	18.9 $\pm$ 5.4

Values for each case are the mean ( $\pm$ SEM) number of tangles in a 250- $\mu$ m-wide cortical traverse (*n* = 10 sections).

<sup>a</sup> ANOVA:  $F_{1,4} = 12.03$ ;  $p = 0.026$ .



**Figure 3.** Thioflavine S staining of neurofibrillary tangles (NFT) and neuritic plaques (NP) in (*A*) area 17, primary visual cortex of the occipital lobe, and (*B*) area 20, higher-order visual association cortex of the inferior temporal gyrus, in the brain from a patient with AD. Roman numerals indicate the cortical layers. Note the large number of NFT in layers III and V, but not in layer IV, of area 20 (*B*). In contrast, no NFT are present in area 17 (*A*). Most of the NP in area 17 (*A*) contain a dense, brightly fluorescent core (NPc type), whereas most NP in area 20 (*B*) lack this core (NPnc type). See Figure 5 for more details on NP type. Calibration bar, 200  $\mu$ m (*A, B*).

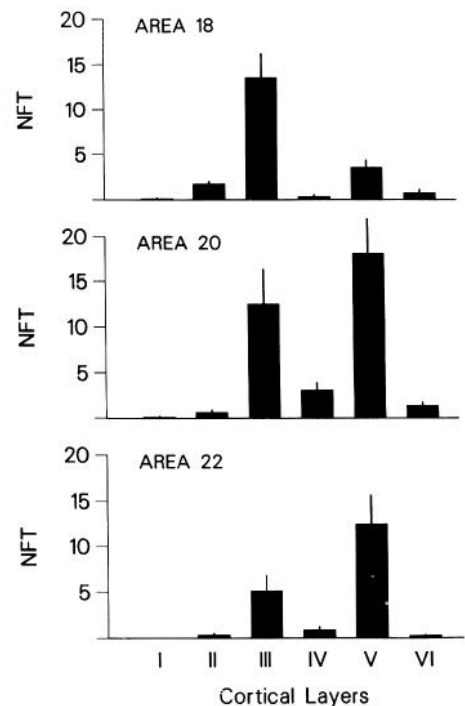
crease in NFT number ( $18.9 \pm 5.4$ ). These differences were present in each of the 5 cases examined (Table 2).

The number of NFT in each area tended to increase in parallel across cases. For example, there was a highly significant positive association between the number of NFT in areas 17 and 18 ( $r = 0.950$ ,  $p = 0.004$ ) and a trend toward a significant correlation between areas 18 and 20 ( $r = 0.766$ ,  $p = 0.076$ ). In addition, the number of NFT in a given region tended to be inversely related to the age of the patient at the time of death. There were strong negative correlations between patient age and the number of NFT in area 17 ( $r = -0.809$ ,  $p = 0.051$ ), area 18 ( $r = -0.941$ ,  $p = 0.005$ ), area 20 ( $r = -0.801$ ,  $p = 0.056$ ), and area 41 ( $r = -0.868$ ,  $p = 0.056$ ) but not area 22 ( $r = -0.440$ , NS).

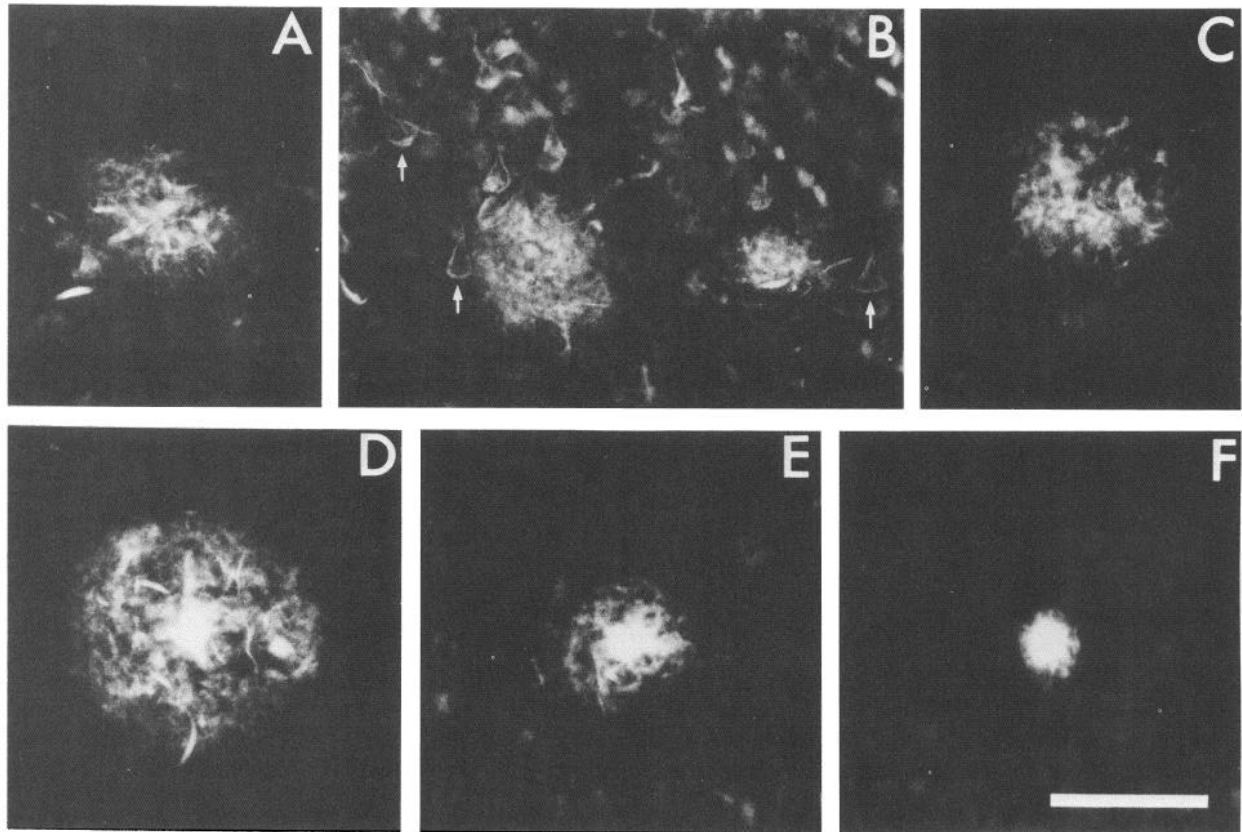
On a laminar basis, NFT were predominantly present in layers III and V (Figs. 3*B* and 4). However, there were striking regional differences in the relative proportion of NFT in these 2 layers. In area 18, layer III contained 79% of the NFT in layers III and V, whereas in area 20, only 41% of the NFT were located in layer III. These differences were highly significant ( $F_{1,5} = 38.19$ ;  $p < 0.002$ ). In addition, area 22 had an even greater shift in the laminar distribution of NFT, such that only 27% of NFT were present in layer III.

#### Neuritic plaques

The morphological appearances of both NPc (neuritic plaque, with core) and NPnc (neuritic plaque, no core) are shown in Figure 5. The regional and laminar distributions of NP were different from, and less specific than, those of NFT. In contrast to the striking differences among visual regions in NFT number, the number of NP was virtually identical across these 3 regions (Table 3). The mean ( $\pm$ SEM) number of NP in a 500- $\mu$ m-wide cortical traverse for 6 cases was  $17.9 \pm 2.2$  in area 17,  $18.2 \pm$



**Figure 4.** Laminar distributions of neurofibrillary tangles (NFT) in area 18 (visual association cortex of the occipital lobe), area 20 (higher-order visual association cortex of the inferior temporal gyrus), and area 22 (auditory association cortex of the superior temporal gyrus) in brains from patients with AD. Bars represent the mean number of NFT in each cortical layer in a 250- $\mu$ m-wide cortical transverse from 6 cases. Values used for each case are the means of 10 sections. Vertical lines represent the SEM.



**Figure 5.** Representative examples of neuritic plaques (NP) as revealed by Thioflavine S staining. NPnc, shown in A–C, lack a dense, deeply fluorescent core, whereas NPc, shown in D–F, contain some degree of a dense, deeply fluorescent core. Arrows in B indicate NFT. Calibration bar, 60  $\mu\text{m}$  (A–F).

1.9 in area 18, and  $21.3 \pm 0.9$  in area 20. Note that a substantial number of NP were present in area 17, a region practically devoid of NFT. A similar dissociation in the presence of NP and NFT was evident in primary auditory cortex.

Although the total number of NP was similar in the 3 visual regions, there were marked differences in the type of NP present in each region (Fig. 6). In area 17, 79% of the NP were of the NPc type, whereas the vast majority of the NP in areas 18 (72%) and 20 (76%) were of the NPnc type. These regional differences in the distribution of each type of NP were present in every case and were highly significant ( $F_{2,10} = 35.87$ ;  $p < 0.0001$ ).

In contrast to NFT, NP number was not associated with the

**Table 3.** Distribution of NP in visual cortical regions of patients with AD

Case	Cortical region		
	17	18	20
4101	$15.6 \pm 1.2$	$18.9 \pm 1.5$	$17.9 \pm 1.3$
4163	$10.6 \pm 1.0$	$12.0 \pm 1.7$	$20.5 \pm 1.5$
4037	$19.5 \pm 1.2$	$19.3 \pm 1.8$	$22.3 \pm 2.8$
5147	$26.0 \pm 2.6$	$26.0 \pm 2.2$	$23.8 \pm 1.4$
1885	$14.8 \pm 1.3$	$17.5 \pm 1.6$	$20.0 \pm 1.8$
4114	$20.9 \pm 1.2$	$15.4 \pm 1.3$	$23.1 \pm 1.7$
Mean <sup>a</sup>	$17.9 \pm 2.2$	$18.2 \pm 1.9$	$21.3 \pm 0.9$

Values for each case are the mean ( $\pm$ SEM) number of plaques in a 500- $\mu\text{m}$ -wide cortical traverse ( $n = 8$  sections).

<sup>a</sup> ANOVA:  $F_{2,10} = 2.76$ , NS.

age of the patient at time of death in area 17 ( $r = -0.328$ , NS), 18 ( $r = -0.021$ , NS), or 20 ( $r = -0.647$ , NS). In addition, no significant correlations were found between NP type and patient age.

The laminar distribution of NP in the 3 visual regions is shown in Table 4. NP were present in all cortical layers but were most numerous in layers III (20%) and IV (46%) of area 17 and in layer III of area 18 (59%) and area 20 (56%). There were also minor differences in the laminar distributions of the 2 NP types. That is, the distribution of NPnc was slightly skewed toward the supragranular layers, whereas the distribution of NPc was slightly skewed toward the infragranular layers.

## Discussion

### Regional and laminar distributions of NFT

Based upon their morphological appearance and laminar distribution, most NFT appeared to be located in the cell bodies of pyramidal neurons, an observation consistent with the reports of previous investigators (see Kemper, 1984, for review; Pearson et al., 1985). On both a regional and laminar basis, NFT exhibited very distinctive and consistent patterns of distribution. In each case of AD we examined, NFT were rarely present in the primary visual cortex, Brodmann's area 17. However, there was a 20-fold increase in the mean number of NFT in the immediately adjacent visual association cortex of area 18 and a further doubling of NFT number in area 20, the higher-order visual association cortex of the inferior temporal gyrus. Thus, the number of NFT progressively increased across areas 17, 18, and 20 in a manner that parallels their position in the proposed

**Table 4. Laminar distribution of NP in visual cortical regions of patients with AD**

Re-gion	Cortical layer						Difference <sup>a</sup>
	I	II	III	IV	V	VI	
17	0.7* (0.2)	0.6* (0.2)	3.6† (0.5)	8.3‡ (1.6)	2.6*† (0.4)	2.3*† (0.4)	$F_{5,25} = 17.31^a$ $p < 0.0001$
18	1.2* (0.2)	1.1* (0.2)	10.8† (1.5)	1.6* (0.4)	2.8* (0.4)	0.9* (0.3)	$F_{5,25} = 33.72$ $p < 0.0001$
20	1.4* (0.5)	2.0* (0.5)	12.0† (0.6)	2.2* (0.3)	2.9* (0.5)	1.0* (0.3)	$F_{5,25} = 74.04$ $p < 0.0001$

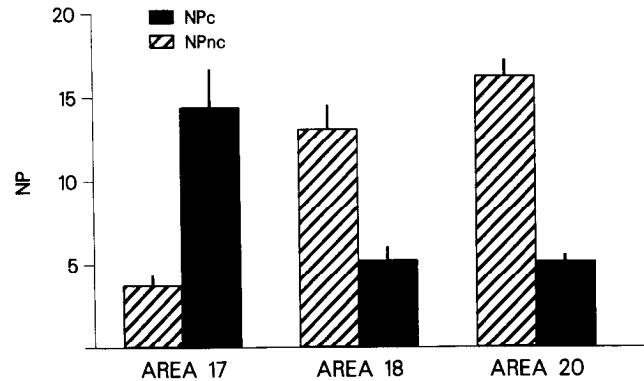
Values are the mean ( $\pm$ SEM) number of plaques in each cortical layer in a 500- $\mu$ m-wide cortical traverse from 6 cases. Values used for each case are the means of 8 sections.

<sup>a</sup> Within each row, values not sharing the same superscript are significantly different ( $p < 0.05$ ).

hierarchical organization of the visual system (Van Essen, 1985). Similarly, in the auditory system, very few NFT were present in primary auditory cortex (area 41), whereas auditory association cortex (area 22) had a greater than 10-fold increase in NFT.

These findings demonstrate a positive correlation between the regional distribution of NFT in AD brains and the distribution of pyramidal neurons that furnish long corticocortical projections (i.e., contralateral and distant ipsilateral projections) in homologous regions of monkey neocortex. For example, in the visual system, primary visual cortex has very few distant ipsilateral efferent projections and even fewer contralateral projections (Tigges et al., 1981; Swadlow, 1983). The immediately adjacent visual association cortex has a substantially greater number of both types of long efferent projections, and the number of such projections increases even more in the higher-order visual association cortex of the inferior temporal lobe (Cragg and Ainsworth, 1969; Zeki, 1969; Jones and Powell, 1970). Similarly, a greater number of long ipsilateral corticocortical projections originate in auditory association cortex than in primary auditory cortex (Pandya et al., 1969).

In every cortical region, NFT were primarily located in layers III and V, the same layers in which long corticocortical projection neurons reside (Jones, 1981, 1984). However, there were marked regional differences in the relative proportion of NFT in these 2 layers. Of the NFT in layers III and V, 79% were present in layer III of area 18, 41% in layer III of area 20, and 27% in layer III of area 22. This shift in the laminar distribution of NFT across cortical regions in AD parallels the laminar shift in the distribution of long corticocortical projection neurons in homologous regions of monkey cortex. For example, the great majority of projections from occipital cortex to temporal lobe originate in layer III (Rockland and Pandya, 1979; Desimone et al., 1980). The majority of neurons that project to the prefrontal cortex from the occipital and inferior and superior temporal regions also resides in layer III. However, the ratio of these neurons in the supra- to infragranular layers progressively decreases from the occipital to the inferior temporal to the superior temporal regions (Barbas and Mesulam, 1981, 1985; Barbas, 1986) in a manner paralleled by the laminar shift in the location of NFT in the homologous regions of human neocortex. In addition, in both the visual and auditory systems of monkey, rostrally directed, "feed-forward" projections to higher-order association regions originate predominantly in layer III, whereas caudally directed, "feedback" projections more frequently arise



**Figure 6.** Distributions of neuritic plaques (NP) in area 17 (primary visual cortex of the occipital lobe), area 18 (immediately adjacent visual association cortex), and area 20 (higher-order visual association cortex of the inferior temporal gyrus) in brains from patients with AD. *Solid bars* represent the mean number of NPc (NP containing any degree of a dense, deeply fluorescent core) and *striped bars* represent the mean number of NPnc (NP lacking a dense, deeply fluorescent core) in each area in a 500- $\mu$ m-wide cortical traverse from 6 cases. Values used for each case are the means of 8 sections. *Vertical lines* represent SEM.

from neurons in the infragranular layers (Galaburda and Pandya, 1983; Van Essen and Maunsell, 1983; Van Essen, 1985). Furthermore, within the hierarchical organization of a given sensory modality, higher-order association regions contain a greater number of neurons furnishing long "feedback" corticocortical projections than do association regions located adjacent to the primary sensory area. Consistent with this laminar organization of long "feedback" corticocortical projections in monkeys, we found that the number of NFT in layer V was 6-fold greater in area 20, the higher-order visual association region of the inferior temporal gyrus, than in area 18, a visual association region located adjacent to primary visual cortex.

It should be noted that layer V pyramidal neurons also give rise to many corticofugal fibers, in addition to corticocortical projections (Jones, 1981, 1984). Although it is possible that NFT develop in layer V neurons that do not furnish long corticocortical projections, regional differences in the number of such neurons have not been reported. However, as indicated above, quantitative data are available on layer V long corticocortical projection neurons, and regional differences in these neurons in monkeys are very similar to the regional differences in layer V NFT in AD brains.

Thus, on both a regional and laminar basis, the distribution of NFT in human neocortex is very similar to the distribution of the subset of pyramidal neurons that furnish long corticocortical projections in monkey cortex. This correlation suggests that NFT reside in the cell bodies of this subclass of pyramidal neurons, and it is consistent with the hypothesis that the dementia of AD results from the degeneration of long corticocortical projection neurons and the loss of the connections they furnish (Morrison et al., 1986a).

Consistent with this hypothesis, and the findings of the present study, are recent reports by Powell and colleagues (Pearson et al., 1985; Esiri et al., 1986). This group also found that there were more NFT in area 18 than in area 17, and that the ratio of NFT in layer III to layer V was greater in area 18 than in area 21 (Pearson et al., 1985). In addition, in a recent non-quantitative study, primary auditory cortex was reported to have fewer NFT than the surrounding auditory association regions (Esiri et al., 1986).

Other lines of evidence also support this hypothesis.

1. The prosomatostatin-derived peptide (PSDP) system of the cortex is profoundly altered in AD, as reflected in decreased tissue levels of PSDP (Davies et al., 1980; Rossor et al., 1980), the presence of PSDP-immunoreactive profiles in NP (Armstrong et al., 1985; Morrison et al., 1985) and a reduction in PSDP receptor number (Beal et al., 1985). Although these findings might suggest that there is a loss of PSDP-containing cortical neurons in AD, the density of cortical PSDP-containing neurons has recently been reported to be normal in this disorder (Nakamura and Vincent, 1986). In addition, cortical levels of neuropeptide Y and GABA, both of which have been shown to coexist with PSDP in cortical neurons (Hendry et al., 1984a, b; Somogyi et al., 1984), are not decreased in AD (Smith et al., 1983; Allen et al., 1984; Perry et al., 1984; Dawbarn et al., 1986). Taken together, these findings suggest that the abnormalities of the PSDP system in AD may reflect a close anatomical relationship between PSDP-containing terminals and those cortical elements that do degenerate in AD. Recent studies of the PSDP system in monkey neocortex have demonstrated that these peptides are present in intrinsic cortical neurons that have patterns of distribution strikingly similar to those of long corticocortical projection neurons (Lewis et al., 1986; Campbell et al., 1987). Thus, the abnormalities of the cortical PSDP system in AD may reflect a synaptic relationship between PSDP-containing processes and the pyramidal neurons that do degenerate in AD (Morrison et al., 1985, 1986a).

2. The cells lost in the cortex of AD brains, the large neurons of layers III and V (Terry et al., 1981; Mann et al., 1985), have the same size and laminar location as the pyramidal neurons that furnish long corticocortical projections (Rockland and Pandya, 1979; Desimone et al., 1980; Barbas and Mesulam, 1981; Jones, 1981, 1984; Van Essen, 1985; Barbas, 1986).

3. The neurotransmitter utilized in corticocortical circuits is believed to be an excitatory amino acid (Baughman and Gilbert, 1981; Fonnum et al., 1981; Hicks and Geddes, 1981). Recent studies have demonstrated in AD the loss of both glutamate (Greenamyre et al., 1985) and aspartate (Palmer et al., 1986) receptors in the neocortex, a profound decrease in glutamate levels in the terminal field of the perforant pathway (Hyman et al., 1986), and the presence of NFT in glutamate-immunoreactive neurons (Maragos et al., 1986).

4. The pattern of pathology in the subiculum and entorhinal cortex described by Hyman et al. (1984), in which the cells connecting the hippocampal formation with association cortices and other structures are affected, may be but one example of a widespread cortical phenomenon in AD.

5. Finally, in immunohistochemical studies of monkey and human neocortex, a monoclonal antibody directed against non-phosphorylated neurofilament protein (N-PNFP) labeled a subpopulation of pyramidal neurons (Morrison et al., 1986b). The laminar and regional distributions of the N-PNFP-immunoreactive cells paralleled the distributions of both long corticocortical projection neurons in monkey neocortex and of NFT in AD. In addition, the presence of NFT in AD specimens was associated with a decrease in the density of N-PNFP-labeled cells compared to controls. These findings support the hypothesis that NFT arise in long corticocortical projection neurons, and they also suggest that the vulnerable cortical cells in AD may contain high intracellular levels of N-PNFP.

Although these data all implicate the long corticocortical projection neurons as the major site of NFT formation, it is possible

that other cortical neurons develop NFT. For example, we found a significant correlation between the numbers of NFT in areas 17 and 18. Consequently, in very severe cases of AD, NFT may be more common in area 17, perhaps arising in the short corticocortical projection neurons of layer III. It is also possible that some NFT are present in somatostatin-containing neurons (Roberts et al., 1985), although we have not been able to confirm this observation (D. A. Lewis and J. H. Morrison, unpublished observations).

#### *Regional and laminar distributions of NP*

In contrast to NFT, NP had different and less specific regional and laminar distributions. On a regional basis, the number of NP did not differ across the proposed hierarchical levels of the visual system (Table 3). Within the auditory system, the number of NP also did not appear to differ substantially between primary and association regions. Thus, in both the primary visual and auditory cortices, NP were clearly present in regions lacking NFT. Although this dissociation strongly suggests that NP and NFT do not arise from the same anatomical elements, the structural components of NFT and NP may still be related. For example, some NP may arise at the terminations of projections from neurons that contain NFT (Suzuki and Terry, 1967; Pearson et al., 1985). These findings also clearly show that primary sensory regions are not spared pathologically in AD, although they lack NFT.

Previous studies have reported that the number of NP appeared to be greater in association than in primary sensory regions (for reviews, see Terry and Katzman, 1983; Kemper, 1984). In addition, in a recent quantitative study, superior frontal and anterior cingulate regions were found to have a greater density of NP than visual and auditory cortical regions (Rogers and Morrison, 1985). Thus, it may be that the distribution of NP is also correlated with the corticocortical systems, although less precisely. That is, the relationship between NP and the corticocortical system may be evident only when comparing the number of NP in regions that differ substantially with regard to the presence of corticocortical projections.

However, it seems most likely that multiple chemical and anatomical systems contribute to NP formation. Cholinergic and catecholaminergic processes, presumably the terminations of afferents from the brain stem, have been identified in simian and human cortical NP (Kitt et al., 1984, 1985; Armstrong et al., 1986). NP-containing fibers immunoreactive for a number of different neuropeptides such as PSDP (Armstrong et al., 1985; Morrison et al., 1985), neuropeptide Y (Chan-Palay et al., 1985; Dawbarn and Emson, 1985), and substance P (Armstrong and Terry, 1985), have also been described in the neocortex from patients with AD. Thus, NP may arise at the terminations of long corticocortical projection neurons, at the terminations of various afferent fibers from the brain stem, such as those from cholinergic or noradrenergic neurons, and from the processes of intrinsic cortical neurons, such as those containing PSDP.

#### *Regional distributions of NP types*

Although the total number of NP was quite similar across the different cortical regions of the visual system, there were marked differences in the type of NP present in each region. Nearly 80% of the NP in primary visual cortex were of the NPc type (i.e., contained a dense, brightly fluorescent core), whereas over 70% of the NP in both areas 18 and 21 were of the NPnc type (i.e., lacked a dense, brightly fluorescent core). Given the criteria

utilized in this study for distinguishing these NP types, all NPnc were probably correctly classified, but it is likely that some NPc were incorrectly identified as NPnc. That is, since the diameter of NP may exceed 100  $\mu\text{m}$ , some proportion of the NP in a 40- $\mu\text{m}$ -thick section will have been cut through a peripheral portion of the NP. Thus, some NPc would have been identified as NPnc because the section counted did not include the core region of the NP. However, this sampling artifact cannot explain the observed differences in distribution of NP types. This type of error in classification is equally likely to occur in all regions of cortex, but more than 50% of the NP in areas 18 and 21, and none of the NP in area 17, would have had to be misclassified in order to account for the observed regional differences. In addition, the regional differences in NP type were present in each case examined.

In previous investigations, NP were described as immature, mature, or burnt-out, based upon their morphological appearance (Terry and Wisniewski, 1970). However, NP have not been demonstrated to undergo a temporally related series of morphological changes. In the present study, immature NP were classified as NPnc, and both mature and burnt-out NP were designated NPc. Instead of representing different stages of NP formation, it may be that the different morphologic appearances of NP reflect different sources of NP formation. Studies to determine the histochemical profile of the neurites in NPc and NPnc are in progress.

#### *Relationship of NFT and NP to age*

We found strong negative correlations between age at time of death and NFT number in 4 of 5 cortical regions, although neither total NP number nor type of NP was significantly associated with age in any of the 3 visual regions. Similarly, in much larger samples of patients (R. D. Terry, unpublished observations), NFT number was inversely related to age in middle frontal ( $n = 95$ ,  $r = -0.450$ ,  $p < 0.001$ ) and inferior parietal ( $n = 93$ ,  $r = -0.575$ ,  $p < 0.001$ ) regions but not in the superior temporal regions ( $n = 98$ ,  $r = -0.180$ , NS). Although the correlations were generally not as strong as with NFT, NP number was also inversely related to age in these regions (middle frontal:  $n = 95$ ,  $r = -0.345$ ,  $p < 0.001$ ; inferior parietal:  $n = 93$ ,  $r = -0.362$ ,  $p < 0.001$ ; superior temporal:  $n = 98$ ,  $r = -0.260$ ,  $p < 0.01$ ). These findings are consistent with previous observations that younger patients with AD have more severe and widespread histological abnormalities (Hubbard and Anderson, 1981; Mountjoy et al., 1983) and a more rapidly progressive clinical course (Sourander and Sjogren, 1970; Seltzer and Sherwin, 1983).

#### **Conclusions**

In conclusion, our findings indicate that NFT and NP have different regional and laminar distributions in the cortical visual and auditory systems of AD brains. NFT exhibit distinctive patterns of distribution that are very similar to the regional and laminar locations of long corticocortical projection neurons in homologous regions of monkey neocortex. This association suggests that the vast majority of NFT reside in the cell bodies of those pyramidal neurons that furnish long corticocortical projections in human neocortex. These findings, in concert with the distribution of (N-PNFP) immunoreactive neurons in primate neocortex (Morrison et al., 1986b), may provide an anatomical and biochemical profile of the cortical neurons that develop NFT in AD. That is, the most vulnerable cells may be the pyramidal neurons that possess long axonal projections termi-

nating in neocortex and that have high intracellular levels of N-PNFP.

In contrast, NP have less distinctive distribution patterns, suggesting a more heterogeneous origin. For example, some NP may arise at the terminations of long corticocortical projections (Suzuki and Terry, 1967; Pearson et al., 1985), whereas others may be formed in the terminal fields of subcortical afferents or intrinsic cortical neurons. This heterogeneity in NP origin, in contrast to the homogeneous origin of NFT, may explain why the severity of dementia (Wilcock and Esiri, 1982) and cortical cell loss (Terry et al., 1981; Mountjoy et al., 1983) in AD are more closely associated with the number of NFT than with the number of NP.

The dementia of AD involves a progressive, global deterioration of intellectual functions, abilities which appear to require the integration of information across many specialized regions of cerebral cortex. The findings of this study may provide an anatomical basis for the loss of intellectual functions in AD, in that they are consistent with the hypothesis that the dementia of AD results from the loss of the structural and functional integrity of the long corticocortical projection systems (Pearson et al., 1985; Rogers and Morrison, 1985; Morrison et al., 1986a). Such a loss would produce a global, cortical disconnection syndrome in which each cortical region functions in isolation.

#### **References**

- Allen, J. M., I. N. Ferrier, G. W. Roberts, A. J. Cross, T. E. Adrain, T. J. Crow, and S. R. Bloom (1984) Elevation of neuropeptide Y (NPY) in substantia innominata in Alzheimer's type dementia. *J. Neurol. Sci.* 64: 325-331.
- Armstrong, D. M., and R. D. Terry (1985) Substance P immunoreactivity within neuritic plaques. *Neurosci. Lett.* 58: 139-144.
- Armstrong, D. M., S. LeRoy, D. Shields, and R. D. Terry (1985) Somatostatin-like immunoreactivity within neuritic plaques. *Brain Res.* 338: 71-79.
- Armstrong, D. M., G. Brucc, L. B. Hersch, and R. D. Terry (1986) Choline acetyltransferase immunoreactivity in neuritic plaques of Alzheimer brain. *Neurosci. Lett.* 71: 229-234.
- Bailey, P., and G. Von Bonin (1951) *The Isocortex of Man*, University of Illinois Press, Urbana, IL.
- Barbas, H. (1986) Pattern in the laminar origin of corticocortical connections. *J. Comp. Neurol.* 252: 415-422.
- Barbas, H., and M-M. Mesulam (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J. Comp. Neurol.* 200: 407-431.
- Barbas, H., and M-M. Mesulam (1985) Cortical afferent input to the principalis region of the rhesus monkey. *Neuroscience* 15: 619-637.
- Baughman, R. W., and C. D. Gilbert (1981) Aspartate and glutamate as possible neurotransmitters in the visual cortex. *J. Neurosci.* 1: 427-439.
- Beal, M. F., M. F. Mazurek, V. T. Tran, G. Chattha, E. D. Bird, and J. B. Martin (1985) Reduced numbers of somatostatin receptors in the cerebral cortex in Alzheimer's disease. *Science* 229: 289-291.
- Brodman, K. (1909) *Lokalisationslehre der Grosshirnrinde*, J. A. Barth, Leipzig, p. 324.
- Campbell, M. J., D. A. Lewis, R. Benoit, and J. H. Morrison (1987) Regional heterogeneity in the distribution of somatostatin-28- and somatostatin-28<sub>1-12</sub>-immunoreactive profiles in monkey neocortex. *J. Neurosci.* 7: 1133-1144.
- Chan-Palay, V., W. Lang, Y. S. Allen, U. Haesler, and J. M. Polak (1985) Cortical neurons immunoreactive with antisera against neuropeptide Y are altered in Alzheimer's-type dementia. *J. Comp. Neurol.* 238: 390-400.
- Cragg, B. G., and A. Ainsworth (1969) The topography of the afferent projections in the circumstriate visual cortex of the monkey studied by the Nauta method. *Vision Res.* 9: 733-747.
- Davies, P., R. Katzman, and R. D. Terry (1980) Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementia. *Nature* 288: 279-280.



- Dawbarn, D., and P. C. Emson (1985) Neuropeptide Y-like immunoreactivity in neuritic plaques of Alzheimer's disease. *Biochem. Biophys. Res. Commun.* 126: 289-294.
- Dawbarn, D., M. N. Rossor, C. Q. Mountjoy, M. Roth, and P. C. Emson (1985) Decreased somatostatin immunoreactivity but not neuropeptide Y immunoreactivity in cortex in senile dementia of Alzheimer type. *Neurosci. Lett.* 70: 154-159.
- Desimone, R., J. Fleming, and C. G. Gross (1980) Prestriate afferents to inferior temporal cortex: An HRP study. *Brain Res.* 184: 41-55.
- Esiri, M. M., R. C. A. Pearson, and T. P. S. Powell (1986) The cortex of the primary auditory area in Alzheimer's disease. *Brain Res.* 366: 385-387.
- Fonnum, F., A. Soreide, I. Kvale, J. Walker, and I. Walaas (1981) Glutamate in cortical fibers. *Adv. Biochem. Psychopharmacol.* 27: 29-41.
- Galaburda, A. M., and D. N. Pandya (1983) The intrinsic architectonic and connective organization of the superior temporal region of the rhesus monkey. *J. Comp. Neurol.* 221: 169-184.
- Greenamyre, J. T., J. B. Penney, and A. B. Young (1985) Alterations in L-glutamate binding in Alzheimer's and Huntington's diseases. *Science* 227: 1496-1500.
- Hendry, S. H. C., E. G. Jones, and P. C. Emson (1984a) Morphology, distribution, and synaptic relations of somatostatin- and neuropeptide Y-immunoreactive neurons in rat and monkey neocortex. *J. Neurosci.* 4: 2497-2517.
- Hendry, S. H. C., E. G. Jones, J. DeFelipe, D. Schmechel, C. Brandon, and P. C. Emson (1984b) Neuropeptide-containing neurons of the cerebral cortex are also GABAergic. *Proc. Natl. Acad. Sci. USA* 81: 6526-6530.
- Hicks, T. P., and R. C. A. Geddes (1981) Synaptic transmission in supra sylvian visual cortex is reduced by excitatory amino acid antagonists. *Can. J. Physiol. Pharmacol.* 59: 893-896.
- Hubbard, B. M., and J. M. Anderson (1981) A quantitative study of cerebral atrophy in old age and senile dementia. *J. Neurol. Sci.* 50: 135-145.
- Hyman, B. T., G. W. Van Hoesen, A. R. Damasio, and C. L. Barnes (1984) Alzheimer's disease: Cell-specific pathology isolates the hippocampal formation. *Science* 225: 1168-1170.
- Hyman, B. T., G. W. Van Hoesen, and A. R. Damasio (1986) Glutamate depletion of the perforant pathway terminal zone in Alzheimer disease. *Soc. Neurosci. Abstr.* 12: 944.
- Jones, E. G. (1981) Anatomy of cerebral cortex: Columnar input-output organization. In *The Organization of the Cerebral Cortex*, F. O. Schmitt, F. G. Worden, G. Adelman, and S. G. Dennis, eds., pp. 199-235, MIT Press, Cambridge, MA.
- Jones, E. G. (1984) Laminar distribution of cortical efferent cells. In *Cerebral Cortex*, Vol. 1, A. Peters and E. G. Jones, eds., pp. 521-553, Plenum, New York.
- Jones, E. G., and T. P. S. Powell (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* 93: 793-820.
- Kemper, T. (1984) Neuroanatomical and neuropathological changes in normal aging and dementia. In *Clinical Neurology of Aging*, M. L. Albert, ed., pp. 9-52, Oxford U. P., New York.
- Kitt, C. A., D. L. Price, R. G. Struble, L. C. Cork, B. H. Wainer, M. W. Becher, and W. C. Mobley (1984) Evidence for cholinergic neurites in senile plaques. *Science* 226: 1443-1446.
- Kitt, C. A., R. G. Struble, L. C. Cork, W. C. Mobley, L. C. Walker, T. H. Joh, and D. L. Price (1985) Catecholaminergic neurites in senile plaques in prefrontal cortex of aged nonhuman primates. *Neuroscience* 16: 691-699.
- Kleinbaum, D. G., and L. L. Kupper (1978) *Applied Regression Analysis and Other Multivariable Methods*, Duxbury, North Scituate, MA.
- Lewis, D. A., M. J. Campbell, and J. H. Morrison (1986) An immunohistochemical characterization of somatostatin-28 and somatostatin-28 (1-12) in monkey prefrontal cortex. *J. Comp. Neurol.* 248: 1-18.
- Mann, D. M. A., P. O. Yates, and B. Marcyniuk (1985) Correlation between senile plaque and neurofibrillary tangle counts in cerebral cortex and neuronal counts in cortex and subcortical structures in Alzheimer's disease. *Neurosci. Lett.* 56: 51-55.
- Maragos, W. F., D. L. Debowey, A. Reiner, A. Rustioni, J. B. Penney, and A. B. Young (1986) Co-localization of Congo red-stained neurofibrillary tangles in glutamate immunoreactive neurons in the hippocampus. *Soc. Neurosci. Abstr.* 12: 442.
- Morrison, J. H., J. Rogers, S. Scherr, R. Benoit, and F. E. Bloom (1985) Somatostatin immunoreactivity in neuritic plaques of Alzheimer's patients. *Nature* 314: 90-92.
- Morrison, J. H., S. Scherr, D. A. Lewis, M. J. Campbell, F. E. Bloom, J. Rogers, and R. Benoit (1986a) The laminar and regional distribution of neocortical somatostatin and neuritic plaques: Implications for Alzheimer's disease as a global neocortical disconnection syndrome. In *The Biological Substrates of Alzheimer's Disease*, A. B. Scheibel and A. F. Weschler, eds., pp. 115-131, Academic, New York.
- Morrison, J. H., D. A. Lewis, M. J. Campbell, G. W. Huntley, D. L. Benson, and C. Bouras (1986b) SMI 32: A potential immunohistochemical marker for the cortico-cortically projecting cells compromised in Alzheimer's disease (AD). *Soc. Neurosci. Abstr.* 12: 943.
- Mountjoy, C. Q., M. Roth, N. J. R. Evans, and H. M. Evans (1983) Cortical neuronal counts in normal elderly controls and demented patients. *Neurobiol. Aging* 4: 1-11.
- Nakamura, S., and S. R. Vincent (1986) Somatostatin- and neuropeptide Y-immunoreactive neurons in the neocortex in senile dementia of Alzheimer's type. *Brain Res.* 370: 11-20.
- Palmer, A. M., A. W. Procter, G. C. Stratmann, and D. M. Bowen (1986) Excitatory amino acid-releasing and cholinergic neurones in Alzheimer's disease. *Neurosci. Lett.* 66: 199-204.
- Pandya, D. N., and E. H. Yeterian (1985) Architecture and connections of cortical association areas. In *Cerebral Cortex*, Vol. 4, A. Peters and E. G. Jones, eds., pp. 3-61, Plenum, New York.
- Pandya, D. N., M. Hallett, and S. K. Mukherjee (1969) Intra- and interhemispheric connections of the neocortical auditory system in the rhesus monkey. *Brain Res.* 14: 49-65.
- Pearson, R. C. A., M. M. Esiri, R. W. Hiorns, G. K. Wilcock, and T. P. S. Powell (1985) Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. *Proc. Natl. Acad. Sci. USA* 82: 4531-4534.
- Perry, E. K., J. R. Atack, R. H. Perry, J. A. Hardy, P. R. Dodd, J. A. Edwardson, G. Blessed, B. E. Tomlinson, and A. F. Fairbairn (1984) Intralaminar neurochemical distributions in human midtemporal cortex: Comparison between Alzheimer's disease and the normal. *J. Neurochem.* 42: 1402-1410.
- Perry, R. H. (1986) Recent advances in neuropathology. *Br. Med. Bull.* 42: 34-41.
- Roberts, G. W., T. J. Crow, and J. M. Polak (1985) Location of neuronal tangles in somatostatin neurones in Alzheimer's disease. *Nature* 314: 92-94.
- Rockland, K. S., and D. N. Pandya (1979) Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.* 179: 3-20.
- Rogers, J., and J. H. Morrison (1985) Quantitative morphology and regional and laminar distributions of senile plaques in Alzheimer's disease. *J. Neurosci.* 5: 2801-2808.
- Rosner, B. (1982) *Fundamentals of Biostatistics*, Duxbury Press, Boston.
- Rossor, M. N., P. C. Emson, C. Q. Mountjoy, M. Roth, and L. I. Iverson (1980) Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of the Alzheimer type. *Neurosci. Lett.* 20: 373-377.
- Schwartz, P. (1972) Amyloid degeneration and tuberculosis in the aged. *Gerontologia* 18: 321-362.
- Seltzer, B., and M. D. Sherwin (1983) A comparison of clinical features in early- and late-onset primary degenerative dementia. One entity or two? *Arch. Neurol.* 40: 143-146.
- Smith, C. C. T., D. M. Bowen, N. R. Sims, D. Neary, and A. N. Davison (1983) Amino acid release from biopsy samples of temporal neocortex from patients with Alzheimer's disease. *Brain Res.* 264: 138-141.
- Somogyi, P., A. J. Hodgson, A. D. Smith, M. G. Nunzi, A. Gorio, and J.-Y. Wu (1984) Different populations of GABAergic neurons in the visual cortex and hippocampus of cat contain somatostatin- or cholecystokinin-immunoreactive material. *J. Neurosci.* 4: 2590-2603.
- Sourander, P., and H. Sjogren (1970) The concept of Alzheimer's disease and its clinical implications. In *Alzheimer's Disease and Related Conditions*, G. W. Wolstenholme and M. O'Connor, eds., Churchill, London.
- Suzuki, K., and R. D. Terry (1967) Fine structural localization of acid phosphatase in senile plaques in Alzheimer's presenile dementia. *Acta Neuropathol.* 8: 276-284.
- Swadlow, H. A. (1983) Efferent systems of primary visual cortex: A

- review of structure and function. *Brain Res. Rev.* 6: 1–24.
- Terry, R. D., and R. Katzman (1983) Senile dementia of the Alzheimer type: Defining a disease. In *Neurology of Aging*, R. Katzman and R. D. Terry, eds., pp. 51–84, Davis, Philadelphia, PA.
- Terry, R. D., and H. M. Wisniewski (1970) The ultrastructure of neurofibrillary tangles and senile plaques. In *Alzheimer's Disease and Related Conditions*, G. E. W. Wolstenholme and M. O'Connor, eds., pp. 145–165, Churchill, London.
- Terry, R. D., A. Peck, R. DeTeresa, R. Schechter, and D. S. Horoupian (1981) Some morphometric aspects of the brain in senile dementia of the Alzheimer type. *Ann. Neurol.* 10: 184–192.
- Tigges, J., and M. Tigges (1985) Subcortical sources of direct projections to visual cortex. In *Cerebral Cortex*, Vol. 3, A. Peters and E. G. Jones, eds., pp. 351–378, Plenum, New York.
- Tigges, J., M. Tigges, S. Ansel, N. A. Cross, W. D. Letbeter, and R. L. McBride (1981) Areal and laminar distribution of neurons interconnecting the central visual cortical areas 17, 18, 19, and MT in squirrel monkey (*Saimiri*). *J. Comp. Neurol.* 202: 539–560.
- Valverde, F. (1985) The organizing principles of the primary visual cortex in the monkey. In *Cerebral Cortex*, Vol. 3, A. Peters and E. G. Jones, eds., pp. 207–257, Plenum, New York.
- Van Essen, D. C. (1985) Functional organization of primate visual cortex. In *Cerebral Cortex*, Vol. 3, A. Peters and E. G. Jones, eds., pp. 259–330, Plenum, New York.
- Van Essen, D. C., and J. H. R. Maunsell (1983) Hierarchical organization and functional streams in the visual cortex. *Trends Neurosci.* 6: 370–375.
- Wilcock, G. K., and M. M. Esiri (1982) Plaques, tangles and dementia. *J. Neurol. Sci.* 56: 343–356.
- Young, W. G., J. H. Morrison, and F. E. Bloom (1985) An electronic morphometry and mapping analysis microscopy system (EMMA) for the quantitative and comparative study of neural structures. *Soc. Neurosci. Abstr.* 11: 679.
- Zeki, S. M. (1969) Representation of central visual fields in prestriate cortex of monkey. *Brain Res.* 14: 271–291.