Orbitofrontal Cortex Pathology in Alzheimer’s Disease

The orbitofrontal cortex has been examined in Alzheimer’s disease (AD) from the viewpoint of neurofibrillary tangle (NFT) pathology, its laminar distribution and topography. NFT pathology in the orbitofrontal cortex is extensive in AD. In cases with extensive cortical pathology, NFTs extend from the pole of the frontal lobe to the orbitoinsular junction. In lesser affected cases, the anterior granular part of the orbital cortex is less invested by NFTs. Layers III and V contain the greatest density of NFTs and these are most dense in the dysgranular areas, posterior to the transverse orbital sulcus. Posterior and medial orbitofrontal areas, forming area 13 and the posterior tip of the paralimbic gyrus, are the most severely damaged, as are the smaller agranular fields that surround the olfactory tract and cortex. The widespread orbitofrontal damage in AD affecting projection neurons suggests that this pathology may contribute heavily to the many non-memory-related behavioral changes observed in this disorder.

Alzheimer’s disease (AD) is a devastating and unremittent neurodegenerative disease with dementia as a certain outcome (Van Hoesen and Damasio, 1987; Braak and Braak, 1991; Hof and Morrison, 1994; Gómez-Isla and Hyman, 1997; Hof, 1997; Davis et al., 1999). Although clearly a disease of the elderly, the appearance of its early pathognomonic signs in autopsies (Braak and Braak, 1997) have caused the suspected onset to be rolled back significantly in recent years and preclinical data, using multiple avenues of assessment, is accumulating (Hof et al., 1992; Davis et al., 1999; De Leon et al., 1999; Price and Morris, 1999).

Historically, AD has largely been considered a disease of the cerebral cortex, although subcortical changes in the cells of origin of pharmacologically specific corticopetal neural systems providing cholinergic, adrenergic and serotonergic input to the cortex have been recognized (Van Hoesen and Damasio, 1987). While these changes provide a rationale for therapeutic interventions to arrest or lessen the symptoms of AD, their role relative to those contributed by the widely damaged cerebral cortex is confounded and remains to be clarified.

In terms of cortical pathology in AD, there is a consensus that the distal association areas of the cortex and the cortex of the limbic lobe bear the brunt of the damage (Van Hoesen and Damasio, 1987; Arnold et al., 1991; Braak and Braak, 1991; Hof and Morrison, 1994). Indeed, this is a prominent feature of gross brain atrophy at autopsy and an unmistakable conclusion microscopically. The primary motor and sensory cortices are largely spared in AD, and even proximal parasympathetic association areas may not be affected until a sizable duration of illness has elapsed. The projection neuron cell types in the association and limbic cortices affected by NFTs in AD are the medium- to large-sized pyramidal neurons that form layers III and V. These neurons give rise to corticocortical association systems and to some corticofugal neural systems that end in the basal ganglia, midbrain and pons. Some investigators have stressed the fact that AD cortical pathology at end-stage illness is analogous to a cortical disconnection syndrome (Hyman et al., 1984; Hof et al., 1990; Hof and Morrison, 1994; Hof, 1997).

Topographically and quantitatively, the greatest cellular changes in AD occur in the temporal lobe, followed closely by the limbic lobe. These pathological observations resonate well with the memory-related cognitive changes in AD. For example, AD pathological changes in the form of NFTs are observed first in the perirhinal cortex (Brodman’s area 35), followed closely by entorhinal cortex (Brodman’s area 28) and the regio inferior (CA 1/subicular) zones of the hippocampal formation (Kemper, 1978; Hyman et al., 1984; Braak and Braak, 1985, 1991; Arnold et al., 1991). Quantitatively these can be extensive in cognitively normal humans (Price and Morris, 1999) but reach a critical number in time and correlate with recent memory changes. Additional NFTs, neuritic plaques and amyloid burden in adjacent inferior and polar temporal cortices signal a more severe impairment, with both recent and remote memory impairments and impending signs of dementia (Hof et al., 1990; Hof, 1997).

While the early and late memory impairments of AD correlate well with temporal lobe pathology, a host of other behavioral changes occur in this illness, and their relationship, if any, to the temporal lobe is far less concrete than disorders of memory. A partial list would include: disinhibition; spatial/construction impairment; autonomic dysregulation; decision making impairments; working memory/confusion; aggressiveness; hallucinations; taste abnormalities; executive control deficits; aphasia; and personality abnormalities. Many of these behavioral changes in AD are in all likelihood associated with other non-temporal divisions of the cortex and/or subcortical structures not yet characterized pathophysiologically (Van Hoesen and Damasio, 1987).

The aim in this report is to focus on the neuropathological changes observed in the orbitofrontal cortex in AD. This poorly understood cortex is thought to play a role in several of the behaviors listed above and AD changes in this area might play a central role in their manifestation (Malloy et al., 1993; Damasio, 1994; Petrides and Pandya, 1994; Pandya and Yeterian, 1996; Price et al., 1996; Rolls, 1996; Chu et al., 1997).

Materials and Methods

We examined the orbitofrontal cortex from 13 brain donors with AD and seven age-compatible controls with no history of neurological or psychiatric disease. The AD group had durations of illness of 3–15 years and ranged in age from 63 to 88 years. Demographics on the AD and control group are summarized in Table 1. All AD donors had been studied before death at the Division of Cognitive Neuroscience, Department of Neurology, University of Iowa Hospitals and Clinics. Their clinical and neuropsychological profile was consistent with AD and a neuropsychological analysis confirmed this illness. Both assessments were consistent...
Within each layer) were calculated in a selected 3 mm window of cortex. The cortical contours of two adjacent sections, cell counts (i.e. the NFTs charted on adjacent sections stained with thioflavin S. By superimposing each cortical layer using a computer-coordinated microscope charting most margin of the orbitoinsular junction area.

The anterior horizontal branch of the Sylvian fissure in the pars orbitalis was lateral to the lateral orbital sulcus between it and the anteriormost tip of the transverse orbital sulcus and another posterior to it. The third location and laterally respectively. The final four locations examined microscopically were the olfactory and medial orbitofrontal sulci bounded these locations medially and laterally respectively. The presumed cytoarchitectural location of areas sampled in AD cases was judged by anterior–posterior and medial–lateral microscopically. The presumed cytoarchitectural location of areas sampled in AD cases was judged by anterior–posterior and medial–lateral microscopically. The presumed cytoarchitectural location of areas sampled in AD cases was judged by anterior–posterior and medial–lateral microscopically. The presumed cytoarchitectural location of areas sampled in AD cases was judged by anterior–posterior and medial–lateral microscopically.

For all brains, the vertebral and internal carotid arteries were cannulated shortly after death and brain removal, and were perfused by syringe with 4% formalin. After as much vascular clearance as possible, the brains were immersion fixed in 4% formalin for 5–10 days. The brain was then sliced into 1 cm coronal slabs and soaked overnight in a solution of 4% formalin, 10% sucrose and 10% glycerol. All coronal slabs containing the orbitofrontal cortex were embedded in a matrix of polyethylene glycol and later sliced on a rotary microtome. Adjacent sections were stained for Nissl substance with thionin and for NFTs and neuritic plaques with thioflavin S.

A quantitative density score was assigned according to the scheme: 0 = 0 NFTs, 1 = 1–10 NFTs/1.6 mm²; 2 = 11–25 NFTs/1.6 mm²; 3 = 26–50 NFTs/1.6 mm²; 4 = 50 NFTs/1.6 mm². The density of NFTs was analyzed statistically. The Ftest was used to test for differences between group means of dysgranular and granular regions. Specific comparison between any two layers was done using Tukey’s post-hoc test. For any layer, specific comparison between regions was done using mean contrasts that were tested by the Ftest. Moreover, comparison of Nissl-stained cell density in AD (n = 13) and control cases (n = 7) was tested by the ttest.

**Results**

**Topography of the Human Orbitofrontal Cortex**
The orbitofrontal cortex of the human and non-human primate brain is extensive and occupies a constant anatomical position over the floor of the anterior cranial fossa dorsal to the thin orbital plate of the frontal bone. Medially, the orbitofrontal cortex extends from a position just caudal to the frontal sinus to a position posteriorly, where it approximates the lamina terminalis. Its anterior and medial parts overlie the lamina cribrosa or cribiform plate, with the olfactory bulb positioned between. Posteriorly, the orbitofrontal cortex is continuous with the cortex that forms the limen insula and a clear demarcation between the two is not apparent. Terminal branches of both the middle and anterior cerebral arteries provide its blood supply.

**Sulcal Topography**
The orbital surface of the human brain is defined medially by the interhemispheric fissure and lateroposteriorly by the anterior horizontal branch of the Sylvian fissure. The conspicuous olfactory sulcus is seen medially and is the most constant sulcus of the orbital surface. The olfactory tract courses over this sulcus until it attaches posteriorly to the orbitofrontal surface and forms the olfactory peduncle. The olfactory sulcus also demarcates the lateral boundary of the paraolfactory gyrus/gyrus rectus. Convention calls for three additional sulci on the orbital surface: typically a prominent medial orbital sulcus running parallel to the olfactory sulcus, a lateral orbital sulcus and a transverse orbital sulcus connecting the medial and lateral orbital sulci (Fig. 1). This pattern is said to form an H-shaped arrangement, although branches of these sulci and numerous secondary sulci often obscure the appearance of a bold ‘H’. While many human brains have some semblance of an H-shaped arrangement of the primary orbital sulci, another common pattern is ‘Y’ shaped, with a short or absent posterior limb to the lateral orbital sulcus (see Figs 2E and 3A–D).

As mentioned already, the paraolfactory gyrus/gyrus rectus extends between the olfactory and interhemispheric fissure. The medial orbitofrontal gyrus is found between the olfactory sulcus and the medial orbital sulcus, and the lateral orbital gyrus is found between the medial and lateral orbital sulci. The pars orbitalis of the inferior frontal gyrus forms a conspicuous area between the lateral orbital sulcus and the anterior horizontal branch of the Sylvian tissue ventral and slightly anterior to the other components of the inferior frontal gyrus, the pars triangularis and pars opercularis. Due to this arrangement, it is always debatable whether the pars orbitalis belongs to the orbitofrontal area or to the ventral part of the dorsolateral prefrontal cortex. As with many parts of the human cerebral cortex, it is essential in the orbitofrontal cortex to pair sulcal patterns with geographic loci for between-brain comparisons.

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Table 1
Cytoarchitecture of the Human Orbitofrontal Cortex and Loci Examined in AD

Cytoarchitectural maps of the orbitofrontal surface are plentiful and date back to Campbell’s early mapping efforts nearly a century ago (Campbell, 1905) (Fig. 2A–E). Brodmann’s efforts on this cortex (Brodmann, 1909, 1914) were not detailed and only two numbers were assigned to this extensive area; area 10 for the polar cortex and area 11 for the remainder. The cortex that forms the pars orbitalis was assigned area 47. In contrast, von Economo and Koskinas parcellated the orbitofrontal cortex in the human brain into as many as 12 areas, taking into account bordering areas in the insulotemporal region (von Economo and Koskinas, 1925). Brodmann’s observations were revised by Beck (Beck, 1949), who added many additional areas. Her efforts were motivated in part by observations made in the non-human primate by Walker (Walker, 1940). More recently additional efforts to bridge the cytoarchitectural characteristics between humans and non-human primates have been made (Preuss and Goldman-Rakic, 1991; Petrides and Pandya, 1994; Semendeferi et al., 1998). Particularly noteworthy are recent reports in the macaque monkey by Carmichael and Price (Carmichael and Price, 1994) and Hof et al. (Hof et al., 1995) in the human where a classical cytoarchitecture analysis has been combined with a modern phenotype analysis of immunohistochemically unique cortical neurons. Both have noted sharper boundaries between areas and a subarea complexity that is substantially greater than that evident by Nissl staining alone.

All considered, there are many generalities that are common to the efforts to characterize the orbitofrontal cortex in cellular terms. The first relates to the fact that the paralactory gyrus/gyrus rectus is formed by cortical fields that have a discernible granularity, or presence of layer IV, anteriorly that diminishes at successively posterior levels. Secondly, Brodmann’s area 47 has been extended medially by most authors and, as exemplified in von Economo and Koskinas’ map detailing their area FF (von Economo and Koskinas, 1925), can be parcellated into many subareas. These authors, along with Beck (Beck, 1949), extend this cortex well into the orbital surface as far medially as the lateral bank of the medial orbital sulcus. Finally, it is the almost unanimous opinion of cytoarchitectural studies that the orbitofrontal cortex has distinct zones based on the development of layer IV. Thus, its anterior areas are highly granular. More posterior areas are dysgranular, with an incipient difficult to find layer IV and a small posterior and medialmost part of the orbitofrontal cortex that is agranular.

Our sampling of the orbitofrontal cortex in AD is not based on cytoarchitecture since we have dealt with pathological tissue, but a synthesis of previous cytoarchitectural efforts has guided us in terms of topography to yield an assurance that most of the major fields were sampled. Additionally, we have conducted extensive study of the cytoarchitecture of all normal control brains. These unpublished observations, and impressions of the cellular structure of the orbital surface, most clearly approximate the efforts of Beck (Beck, 1949) and von Economo and Koskinas (von Economo and Koskinas, 1925). Also, they would be compatible, in large part, with the views of Hof et al. (Hof et al., 1995), although these authors appear to attribute too much of the posterior orbitofrontal surface to the agranular cortical category.

The thirteen loci we have sampled include four along the midline (Fig. 3A). These were the anterior granular part of the paralactory gyrus termed APOg, a more posterior paraolfact-
ory granular area termed PPOg, an anterior paraolfactory gyrus area distinctly dysgranular termed APoDg and a posterior para-olfactory gyrus area termed PPOdg that is dysgranular/agranular. The anterior three loci all continue medially onto the medial wall of the hemisphere while locus PPOdg continues medially with the dysgranular and agranular subdivisions of area 25.

Anterior and lateral to the olfactory sulcus four additional loci were examined. Area 11m is a granular cortex anterior and medial to the anterior tip of the olfactory sulcus. Area 11a forms a granular cortex along the anterior half of the medial orbital gyrus, while 11p, a dysgranular cortex, forms its posterior half. The ventromedial part of the orbitofrontal surface, just anterior to the junction with the anterior ventral insular cortex, is distinctly dysgranular and termed area 13dg. One locus was sampled at the anterior pole of the orbitofrontal cortex in highly granular cortex and termed area or locus 10.

Three loci were examined in the lateral orbital area both anterior and posterior to the transverse orbital sulcus. Area 47a was an area of granular cortex lateral to the medial orbital sulcus and anterior to the transverse orbital sulcus. Area 47p was located posterior to the transverse orbital sulcus and was a dysgranular cortex with an ill-defined and incipient layer IV. A distinctly dysgranular/agranular area lateral to the orbitoinsular junction was termed 47dg. Finally, the anterior part of the pars orbitalis lateral to the lateral orbital sulcus was sampled and termed area 47L.

Laminar Distribution and Topography of AD Pathology in Orbitofrontal Cortex

The mean densities of NFTs in each cortical layer were determined for the 13 loci sampled on the orbitofrontal surface for the 13 AD and seven control cases (Figure 3B–D and Table 2). The latter had no appreciable pathology other than an occasional NFT and diffuse plaque. However, all AD cases had orbitofrontal pathology and distinct patterns of NFTs. The differential laminar distribution of NFTs was a striking result. In all cases these were confined to layers III and V, with lesser involvement of layer VI (Figs 3B–D and 4A–B). The latter was present in cases with heavy quantities of pathology, but was often absent entirely in cases with lesser quantities of NFTs. Although a few NFTs were seen in layer I, it was a rare observance. For all loci examined, layer V NFTs were more dense in number than any other cortical layer ($P < 0.001$), followed by layers III and VI. It was striking in the charted reconstructions of cross-sections in heavily affected cases to find a bilaminate pattern of NFTs in layers III and V across the entire orbitofrontal surface (Fig. 4A). These extended from its pole anteriorly to its junction posteriorly with the orbitoinsular cortex, and from the apex of the paraolfactory gyrus medially to the anterior horizontal limb of the Sylvian fissure laterally. In such cases NFT distribution was remarkably regular in layer V, with no apparent groupings or modules of affected neurons. The same was true for layer III; however, occasional patchiness was observed in this layer, and occasionally NFTs...
were grouped. Consistent patterns of this variety, though, were never observed within or across cases. Although the differential laminar distribution of NFTs in layers III and V was an invariant feature of all orbitofrontal loci sampled, the density of changes within these layers varied in accordance with loci. The lowest mean density of NFTs for layer V for the orbital surface was observed in the polar parts, and to a similar degree in those loci lateral to the medial orbital sulcus and anterior to the transverse orbital sulcus. These would include granular cytoarchitectural areas 10, 11m and 47a.

The paraolfactory gyrus cortical areas had mixed involvement of layer V anteriorly. In its granular subdivisions APOg and PPOg, NFT density was moderate. However, in its posterior parts, loci APOdg and PPOdg, which are dysgranular areas, with a weak and incipient layer IV, NFTs increased in number dramatically in eight of the 13 cases examined irrespective of the duration of illness. This was especially dramatic for locus PPOdg, whose density of NFT doubled, tripled and quadrupled paraolfactory areas successively anterior to it. The posterior part of the medial orbital gyrus, which we term locus 13, was also heavily invested by NFTs, having nearly twice the mean density of medial orbital gyrus areas anterior to it (Fig. 5).

The NFT mean density for layer V for cortical locus 47p caudal to the transverse orbital sulcus and lateral to the lateral orbital sulcus was moderate and only slightly greater than the granular areas in the frontal pole. This large region of dysgranular cortex, however, had variable quantities of NFTs in layer V, with fewer changes in some cases and dense changes in others. These were not as dense overall as dysgranular areas medial and posterior to it, as described above, but comparable in cases with heavy pathology.

A somewhat similar observation and hierarchy of NFT mean density per locus was observed for layers III and VI, although these layers were less affected than layer V in all cases. Generally the posterior loci along the paraolfactory gyrus and medial orbital gyrus had higher mean densities of NFTs in layers III and V than granular areas that lie anterior to them. Statistical comparisons revealed highly significant differences \((P < 0.001)\) in mean NFT density for layers III and V for all comparisons between loci in dysgranular cortices versus granular cortices.

### Discussion

As is apparent from gross brain inspection alone at autopsy, the orbitofrontal cortex is damaged conspicuously in AD. To the eye,

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Standard deviations are shown in parentheses.

Figure 4. Neurolucida chartings of a cross-section through the orbitofrontal cortex in an AD case depicting the topography and laminar distribution of NFTs (A) and diffuse and neuritic plaques (B). Note in (A) the bilaminate patterns in layers III and V and the intense quantities in layer V of dysgranular areas 11p and 47p. Note in (B) that neuritic and diffuse plaques are more widely spread across all cortical layers and denser in quantity in areas 11p and 47p. Sulcal labeling is identical to that described for Figure 1. The cross-sectional level of cut for these chartings is shown in Figure 1.
this involves a widening of sulci and a flattening and atrophy of gyri. Posteriorly and medially it is not unusual to observe a discoloring of the cortex. Microscopically, most of the orbitofrontal cortex contains NFTs in layers III and V in cases with heavy pathology, and with pathological staining these form dense ribbons anteriorly to posteriorly and laterally to medially. Layer V is especially prominent for its number of NFTs and for paired helical filaments that extend for long distances into the apical dendrites of these large pyramidal neurons (Fig. 6). The anterior and medial granular orbitofrontal cortex, corresponding to Brodmann’s areas 10 and 11, and the anterior half of the paraolfactory gyrus in some AD cases, may be relatively spared, with only occasional NFTs in layers III and V. However, all of the cases we have studied contained NFTs in the dysgranular posterior and medial orbitofrontal cortex. The lateral and posterior parts of the orbitofrontal dysgranular cortex, corresponding to what we have termed area 47p, had variable degrees of pathology. Hof et al. (Hof et al., 1995) have pointed out that the transverse orbital sulcus is a limiting sulcus roughly dividing the orbital cortex into granular areas anteriorly and dysgranular areas posteriorly. We agree with this observation since this sulcus in AD often seemed to divide a more modest quantity of NFTs in granular cortex anteriorly from a greater quantity of NFTs in dysgranular cortex posteriorly. However, within the latter, posterior and medial dysgranular orbitofrontal cortices had highly dense quantities of NFTs.

The high quantity of NFTs in layers III and V corresponds well with observations in other cortical association areas in AD. As pointed out by Hof and Morrison (Hof and Morrison, 1994, 1996), these pyramidal neurons are the origin for many neural systems of the cerebral cortex, including intra- and interhemispheric corticocortical association systems and corticofugal systems that course to the pons and to the striatum. The heavy involvement of posterior and medial orbitofrontal cortices in AD would suggest also that the ventral striatum and magnocellular nuclei of the basal forebrain would also be deprived of orbitofrontal cortex input (Mesulam and Mufson, 1984; Haber et al., 1995).

In addition to the pathways mentioned above, a number of recent investigations in non-human primates have clarified the organization of the cortical connections of the amygdala and hypothalamus (Amaral and Price, 1984; Barbas, 1988, 1993; Barbas and De Olmos, 1990; Carmichael and Price, 1995; Price et al., 1996; Öngür et al., 1998; Rempel-Clower and Barbas, 1998). Many of these neural systems involve the posterior and medial parts of the orbitofrontal cortex and the pyramidal neurons that in humans have NFTs in AD. In view of the high mean density of NFTs in these orbitofrontal areas in all cases

Figure 5. Photomicrograph of thioflavin S-stained areas of the orbitofrontal cortex showing the laminar distribution of NFTs (bar = 200 µm.) In (A), (C) and (D) arrows point to neuritic plaques.

Figure 6. NFTs in layer V of the dysgranular area 47p of the orbitofrontal cortex caudal to the transverse orbital sulcus stained with thioflavin S.
of AD, it is likely that amygdaloid, and to some degree hypothalamic, neural systems that arise and end here would be the most greatly altered in the disorder.

The list of functional correlates associated with the orbitofrontal cortex is large, covering a diversity of behaviors from sensory-related mechanisms associated with taste and olfaction to decision making, mood, social behavior and aggressiveness and personality (Butter and Snyder, 1972; Van Hoesen et al., 1980; Goldman-Rakic, 1988; Damasio et al., 1990; Damasio, 1994; Rolls, 1996). A large classic literature, still in many respects unclarified, links it to blood pressure and respiratory regulation, and even gastric motility (Spencer, 1894; Bailey and Sweet, 1940; Delgado and Livingston, 1948; Livingston et al., 1948a,b; Chapman et al., 1949, 1950; Kaada et al., 1949).

Aside from physiological and imaging efforts related to taste and olfaction (Tanabe et al., 1975; Takagi, 1986, 1991; Zatorre et al., 1992; Rolls and Baylis, 1994; Rolls et al., 1999; Scott et al., 1999), localization of function within the orbitofrontal cortex has not been readily achievable. In this respect, it will be difficult in AD to isolate exact functional correlates since the pathology is widespread and heavily involves the neurons that form linkages and neural systems with other cortical areas (Cavada and Goldman-Rakic, 1989a,b). Hope for a more discrete functional analysis of the orbitofrontal cortex is embodied in the recent anatomical research findings of Price and his students in the monkey (Price et al., 1996) and the Hof et al. findings in the human (Hof et al., 1995). The diversity of subareas they observe might be predicted given the complex panorama of behaviors attributed to the orbitofrontal cortex. However, AD pathology would appear to cut across this organization. Nevertheless, it is probably useful to recognize that the non-memory-related behavioral changes in AD are substantial in number, and in many instances are likely due to disruption of widespread cortical and subcortical neural systems that involve the orbitofrontal cortex.

Notes

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