Systematic Regional Differences in the Cholinergic Innervation of the Primate Cerebral Cortex: Distribution of Enzyme Activities and Some Behavioral Implications

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Choline acetyltransferase and acetylcholinesterase enzymatic activities were measured in 33 cytoarchitectonic subregions of the cerebral cortex in two rhesus monkeys. As expected, the hippocampus and amygdala were rich in these enzymes. In addition, the paralimbic (mesocortical) regions of the brain (e.g., parahippocampal, insular, caudal orbitofrontal, and temporopolar areas) also contained high levels of both enzymes. In contrast, the concentration of these cholinergic markers was the lowest within all frontal and temporoparietal association areas. As a group, the primary sensory and motor regions contained an intermediate level of choline acetyltransferase activity. Both cholinergic markers also showed a gradual increase from the isocortical toward the more primitive periallocortical subsectors of paralimbic areas. These anatomical patterns have potential implications for the role of cholinergic pathways in the memory process and in the pathogenesis of Alzheimer's disease.

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The cholinergic innervation of the neocortex, and the nucleus basalis from which this innervation is derived, both show marked pathological changes in patients with Alzheimer's disease and in parkinsonian patients who are also demented [5, 6, 20, 32, 33, 35, 37, 38, 41]. These are not the only or even the predominant pathological findings in either of these degenerative conditions. However, the depletion of cortical cholinergic input has been implicated in the pathophysiology of the dementia as this transmitter is known to play a prominent role in many aspects of arousal, mood, and memory [2, 8, 13a, 15, 22]. The anatomical organization of cholinergic projections from the nucleus basalis to the neocortex has been investigated in extensive detail in the primate brain [25, 28, 31]. These projections are topographically organized and they reach all cortical areas, without any known exception. However, with the exception of a few reports on the subject [18, 42], there is much less systematic information about the regional distribution of this cholinergic innervation upon the vast surface of the cytoarchitectonically heterogeneous neocortical mantle. The details of this distribution are of obvious relevance as the more complex behavioral effects associated with cholinergic pathways are likely to be exerted at the cortical level.

The enzyme acetylcholinesterase (AChE) has often been used as a marker of cortical cholinergic innervation. Studies based on AChE histochemistry in the rat and cat have shown that the limbic and olfactory areas contain higher AChE staining intensities than other cortical areas [17, 36]. In the cortex of the rhesus monkey we observed that AChE staining was light in association areas, most intense in limbic and paralimbic areas (with the exception of the cingulate gyrus), and intermediate within the primary sensory and motor areas [23, 27]. Within the heterogeneous architecture of paralimbic areas (e.g., insula, orbitofrontal cortex, temporal pole, parahippocampal gyrus), we also observed that the AChE staining intensity gradually increased from the isocortical component toward the less differentiated nonisocortical sector. Although these histochemical patterns could reflect parallel variations in the density of cortical cholinergic innervation, it is important to note that histochemical staining intensity is

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not linearly related to enzyme activity and that AChE (which is also present in noncholinergic neurons) is only an indirect marker for cholinergic innervation. Therefore, we decided to test the hypotheses suggested by these histochemical staining patterns using quantitative determinations of regional AChE and choline acetyltransferase (ChAT) activities. These studies, upon which this report is based, confirmed that there are marked regional variations in cortical cholinergic activity, that these variations obey cytoarchitectonic boundaries, and that they parallel the regional differences demonstrated by AChE histochemistry.

Methods

Two juvenile male rhesus monkeys (approximately 2 kg in weight) were studied. Each animal was deeply anesthetized with pentobarbital (35 mg/kg) and placed on a stereotaxic head holder. The calvarium, occipital bone, and spinous processes of the upper cervical vertebrae were removed. Cardiopulmonary arrest was induced by a medullary transection. The brain was then rapidly removed, placed in chilled (4°C) 0.1 M phosphate buffer at pH 7.4, and sectioned coronally into 2- to 5-mm slabs along a line of cut similar to the one used in our histochemical experiments [27]. A list of 33 key cytoarchitectonic areas was compiled to test the validity of the patterns identified during histochemical analysis. The regions of interest were identified by matching the topographical features of the fresh brain slabs to those of the cytoarchitectonic maps prepared from AChE- and Nissl-stained material. To maximize uniformity, each of the 33 samples was obtained from the center of the target cytoarchitectonic region, was kept small (50 to 200 mg), contained only gray matter, and was derived from equivalent parts of both hemispheres. The sample was weighed, homogenized in chilled 0.1 M phosphate with 0.5% (v/v) triton X-100, and immediately frozen in dry ice. The ChAT assays were done in triplicate [12] and the AChE assays in duplicate or triplicate [10], depending on the size of the sample. The protein was measured by the method of Wang and Smith [40]. As ChAT is the more specific marker for cholinergic innervation, the activity levels of this enzyme provided the basis for the major conclusions. Each of the two cases was considered as an independent experiment for testing the specific predictions that had been derived from the AChE histochemical observations.

Results

Some cytoarchitectonic considerations are reviewed briefly to clarify the principles that guided the selection of the samples and the subsequent data analysis (see [21] for further detail). The hemispheric surface of the human and monkey brain can be subdivided into at least four major types of cortex: (1) the corticoid-allocortical formations (e.g., hippocampus, amygdaloid complex), also known as the *core limbic structures;* (2) the paralimbic (mesocortical) formations of the insula, temporal pole, caudal orbitofrontal cortex, parahippocampal region, and cingulate complex; (3) the six-layered, well-granularized homotypical association cortex of the prefrontal and temporoparietal areas; and (4) the primary sensory and motor areas.

The paralimbic areas have the most heterogeneous architecture as they provide a transitional bridge from the primitive allocortex to homotypical association cortex. In fact, each of the five paralimbic areas of the primate brain can be subdivided into two major components: a nonisocortical component that is adjacent to the allocortex and a more differentiated isocortical (granular) component that is adjacent to the homotypical association cortex. The nonisocortical component in the temporopolar, insular, and orbitofrontal paralimbic formations has been further subdivided into an intermediate peri-isocortical (dysgranular) sector and a more primitive periallocortical (agranular) sector. In the parahippocampal region, we included the entorhinal and prorhinal areas within the nonisocortical component, and the adjacent medial inferotemporal cortex (TEm) was considered as an isocortical component of this paralimbic region. The parolfactory gyrus constitutes a subcallosal continuation of the cingulate paralimbic complex and contains one of its most important nonisocortical components. These are the considerations that led to the selection of samples (see Figure 1 for their location) and to their classification as shown in the Table. The cingulate gyrus was classified separately (Group C in the Table) because our previous AChE histochemical experiments had shown that its staining pattern was not entirely analogous to that of the other paralimbic regions.

Two independent but complementary analyses were employed. First, the ChAT-specific activities of the 31 samples in Groups A to E of the Table were divided into four nonoverlapping ranges. Figure 1 shows this type of analysis for Case 1. As illustrated in Figure 1, all of the homotypical association areas and the primary sensorimotor areas (Groups A and B in the Table) fall within the two lowest ranges of ChAT activity. The cingulate cortex (Group C in the Table) also belongs in these two ranges. On the other hand, except for the dysgranular midorbitofrontal area (Sample 25), the nonisocortical paralimbic sectors (Group E in the Table) have ChAT activities within the highest two ranges of enzyme activity.

Figure 1 also shows that the paralimbic areas tend to display an internal gradient of ChAT activity that parallels the cytoarchitectonic transitions: in general, the more primitive the cortex (i.e., the closer it is to core limbic structures), the higher its ChAT content. For example, periallocortical (agranular) sectors of orbitofrontal (Sample 26 in Figure 1), temporopolar (Sample 30), and insular cortex (Sample 28) each had higher ChAT activity than the immediately adjacent peri-isocortical (dysgranular) sectors (Samples 25, 29, and

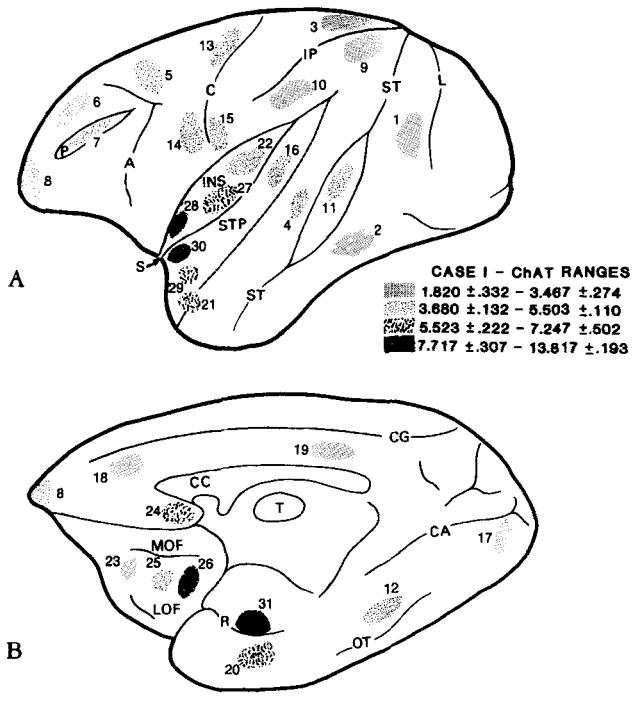

Fig 1. Regional choline acetyltransferase (ChAT) *activities of Samples 1 to 31 in Case 1 have been divided into four nonoverlapping ranges. The sample numbers correspond to those in the Table. (A) Lateral view of the hemisphere. (B) Medial and ventral view. The* dashed line *in the temporal lobe indicates the boundaries of the supratemporal plane* (STP) *and is not a true sulcal marking.* (A = *arcuate sulcus;* C = *central sulcus;* CA = *calcarine sulcus;* CC = *corpus callosum;* CG = *cingulate sulcus;* INS = *insula;* IP = *intraparietal sulcus;* L = *lunate sulcus;* LOF = *lateral orbitofrontal sulcus;* MOF = *medial orbitofrontal sulcus;* OT = *occipitotemporal sulcus;* P = *principal sulcus;* R = *rhinal sulcus;* S = *sylvian fissure;* ST = *superior temporal sulcus;* T = *thalamus.)*

27, respectively). In the insular and orbitofrontal cortex the ChAT activities of the peri-isocortical (dysgranular) sectors (Samples 27 and 25, respectively) were in turn higher than in the adjacent isocortical (granular) sectors (Samples 22 and 23, respectively). In the medial temporal paralimbic zone, the ChAT activity was higher in the nonisocortical entorhinal–prorhinal sector (Sample 31) than in the adjacent isocortical TEm sector (Sample 20). Within the cingulate complex, the ChAT activity was higher in the nonisocortical parolfactory area (Sample 24) than in the more dorsal cingulate gyrus (Samples 18 and 19). In the temporopolar region, however, the isocortical (granular) sector (Sample 21) belonged to the same range of ChAT activity as the adjacent peri-isocortical (dysgranular) region (Sample 29). The individual values in Case 2 showed a similar set of relationships to those of Case 1 even though there were some isolated differences in detail (see Table). For example, the ChAT activity of the primary auditory area (Sample 15) was unexpectedly high in Case 2 and the temporopolar isocortical (granular) region of Case 2 had a higher enzyme activity than the peri-isocortical (dysgranular) temporopolar sector. The overall pattern of regional differences in enzyme activity was remarkably similar in the two experiments, however, as shown by a correlation of 0.88 ($p < 0.001$) between the corresponding ChAT values of the 33 samples in the two cases.

The analysis of Figure 1 is based on a strict rank order of the ChAT specific activity in each of the sampled areas. A second type of analysis was carried out by separating the 33 regions into six categories (Table). The ChAT mean specific activity was lowest in Groups A (association areas) and C (cingulate gyrus), higher than A in Group B (primary sensorimotor regions), higher than B in Group D (isocortical components of paralimbic zones), even higher in Group E (nonisocortical components of paralimbic zones), and highest in Group F (core limbic areas). An analysis of variance with the Orthogonal Comparisons Test showed that these differences were statistically significant ($p < 0.005$) in each of the two cases. The amygdala consistently had a ChAT specific activity higher than that in any other cortical region including the hippocampus.

Several comparison areas were also sampled. As expected, the corpus callosum and the cerebellum had very low ChAT levels. The nucleus basalis and the putamen are known to be among the areas with the highest ChAT activites; this is consistent with the values in the Table. In contrast to the cortical surface and the amygdala, where the ChAT is present predominantly, if not exclusively, within axons, the putamen and the nucleus basalis also contain cholinergic cell bodies that synthesize ChAT, and this may account for the high ChAT activity in these two regions [26]. The high intensity of ChAT in the amygdala is particularly impressive as it reflects, almost exclusively, the density of terminal and preterminal cholinergic fibers.

The regional variations of AChE activities in the 33 sampled areas were very closely correlated with the variations of ChAT activity ($r = 0.97$, $p < 0.001$ in Case 1; $r = 0.89$, $p < 0.001$ in Case 2). Groups A, B, and C did not show consistent differences of mean AChE activity. However, the other group differences in AChE as well as the interareal gradients within paralimbic zones were in exactly the same direction as those shown by regional ChAT activities (Table). These results are in agreement with AChE histochemical observations (Fig 2).

Enzyme Specific Activities and Standard Errors[a,b]

Sample No., Area[c]	Case 1 ChAT (nmol/15 min/mg protein)	Case 1 AChE (μmol/hr/mg protein)	Case 2 ChAT (nmol/15 min/mg protein)	Case 2 AChE (μmol/hr/mg protein)
A. Association areas	**3.465 ± 0.278**	**0.898 ± 0.074**	**7.202 ± 0.790**	**0.832 ± 0.387**
1. (OA, OB) Peristriate visual association	3.467 ± 0.274	1.165 ± 0.068	3.938 ± 0.186	0.260 ± 0.010
2. (TE) Temporal visual association	1.820 ± 0.332	1.046 ± 0.080	5.560 ± 0.077	0.600 ± 0.020
3. (PE) Somatosensory association	3.213 ± 0.162	0.688 ± 0.130	4.327 ± 0.043	1.004 ± 0.015
4. (TA) Auditory association	4.357 ± 0.047	1.064 ± 0.075	9.081 ± 0.520	1.170 ± 0.150
5. (FB) Dorsal premotor association	3.990 ± 0.336	1.034 ± 0.094	9.708 ± 0.466	1.120 ± 0.007
6. (FD) Dorsolateral prefrontal	2.740 ± 0.075	0.418 ± 0.111	6.096 ± 0.208	0.950 ± 0.030
7. (FD) Principalis cortex (prefrontal)	3.680 ± 0.132	0.926 = 0.096	6.758 ± 0.014	0.720 ± 0.056
8. (FD) Frontopolar cortex	4.157 ± 0.162	1.194 ± 0.010	5.827 ± 0.290	1.190 ± 0.004
9. (PG) Caudal inferior parietal lobule	2.070 ± 0.123	0.501 ± 0.047	4.092 ± 0.225	0.290 ± 0.015
10. (PF) Rostral inferior parietal lobule	2.867 ± 0.132	0.708 ± 0.208	11.320 ± 0.144	0.390 ± 0.007
11. Banks of superior temporal sulcus	4.157 ± 0.113	0.977 ± 0.065	11.707 ± 0.470	0.830 ± 0.110
12. (TF) Caudal inferotemporal cortex	5.047 ± 0.283	1.068 ± 0.005	8.002 ± 0.039	1.460 ± 0.007
B. Primary sensorimotor regions	**4.394 ± 0.576**	**0.979 ± 0.154**	**9.820 ± 3.068**	**0.546 ± 0.382**
13. (FA) Dorsal primary motor	4.013 ± 0.084	0.988 ± 0.042	6.335 ± 0.255	0.540 ± 0.012
14. (FBA-FA) Ventral primary motor	5.443 ± 0.154	0.863 ± 0.050	7.191 ± 0.070	0.535 ± 0.005
15. (PC[3b]) Primary somatosensory	5.503 ± 0.110	1.566 ± 0.005	10.511 ± 0.480	0.540 ± 0.008
16. (TC) Primary auditory	4.653 ± 0.177	0.778 ± 0.069	21.307 ± 1.213	1.100 ± 0.060
17. (OC) Primary visual	2.367 ± 0.124	0.702 ± 0.157	3.762 ± 0.078	0.016 ± 0.001
C. Cingulate gyrus	**3.170 ± 0.130**	**0.662 ± 0.008**	**7.600 ± 1.440**	**0.755 ± 0.544**
18. (LA) Anterior cingulate	3.040 ± 0.310	0.656 ± 0.139	9.043 ± 0.507	1.144 ± 0.090
19. (LC) Caudal cingulate	3.300 ± 0.134	0.672 ± 0.069	6.158 ± 0.126	0.370 = 0.008
D. Isocortical paralimbic areas	**5.405 ± 0.775**	**1.015 ± 0.071**	**14.358 ± 3.166**	**1.125 ± .341**
20. (TEm) Medial inferotemporal visual association	5.523 ± 0.222	1.144 ± 0.070	11.268 ± 0.564	1.550 ± 0.230
21. (*STPg*-Anterior TA) Temporopolar auditory association	7.247 ± 0.502	0.890 ± 0.164	23.366 ± 0.182	1.240 ± 0.220
22. (*Ig*) Granular insula	5.387 ± 0.122	1.134 ± 0.066	13.870 ± 0.533	0.920 ± 0.060
23. (*OFg*) Granular anterior orbitofrontal	3.457 ± 0.156	0.892 ± 0.036	8.933 ± 0.142	0.790 ± 0.190
E. Nonisocortical paralimbic zones	**8.686 ± 1.280**	**1.809 ± 0.259**	**17.282 ± 2.162**	**1.951 ± 0.734**
24. (FL) Parolfactory area	6.670 ± 0.326	1.566 ± 0.223	9.574 ± 0.311	1.706 ± 0.170
25. (*OFdg*) Dysgranular midorbitofrontal	5.147 ± 0.135	0.964 ± 0.026	14.282 ± 0.395	0.950 ± 0.030
26. (*OFap*) Agranular caudal orbitofrontal	13.733 ± 1.025	3.050 ± 0.160	28.754 ± 1.133	3.260 ± 0.200
27. (*Idg*) Dysgranular insula	5.703 ± 0.136	1.430 ± 0.118	15.358 ± 0.683	1.240 ± 0.020
28. (*Iap*) Agranular insula	7.717 ± 0.307	1.624 ± 0.015	22.827 ± 0.675	1.820 ± 0.060
29. (*TPdg*) Dysgranular temporopolar	5.767 ± 0.350	1.326 ± 0.040	18.418 ± 0.233	2.640 ± 0.010
30. (*TPap*) Agranular temporopolar	13.817 ± 0.193	2.872 ± 0.281	16.850 ± 0.442	1.870 ± 0.180
31. Entorhinal-prorhinal	10.927 ± 0.513	1.700 ± 0.006	12.206 ± 0.281	2.070 ± 0.230
F. Core limbic areas	**21.675 ± 12.795**	**3.960 ± 2.160**	**39.730 ± 11.850**	**5.220 ± 3.323**
32. Midhippocampus	8.883 ± 0.613	1.799 ± 0.099	27.878 ± 0.340	2.870 ± 0.030
33. Amygdala	34.470 ± 2.023	6.122 ± 0.429	51.582 ± 1.128	7.570 ± 0.150
Comparison areas				
Nucleus basalis	37.527 ± 1.292	10.068 ± 0.150	41.050 ± 2.555	8.990 ± 0.230
Putamen	45.380 ± 1.300	6.749 ± 0.718	46.477 ± 1.200	18.550 ± 1.290
Corpus callosum	1.670 ± 0.071	0.611 ± 0.093	3.578 ± 0.092	0.014 ± 0.002
Cerebellum	0.210 ± 0.150	3.354 ± 0.144	1.012 ± 0.017	3.950 ± 1.480

[a]The anatomical locations of the sampled areas 1–31 are shown in Figure 1.
[b]Values in bold type indicate group means.
[c]Letters in parentheses indicate the cytoarchitectonic designation of the cortical areas. Italicized letters refer to the architectonic designation of Mesulam and Mufson [23]; the others are according to von Bonin and Bailey [4].

ChAT = choline acetyltransferase; AChE = acetylcholinesterase.

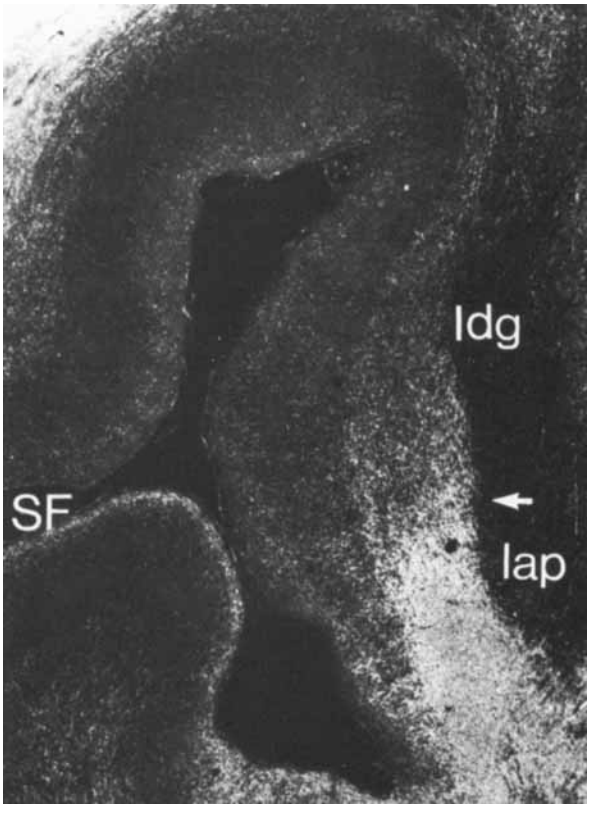

Fig 2. Darkfield photomicrograph of acetylcholinesterase (AChE) histochemical staining within the rhesus monkey insula. The white arrow *designates the architectonic boundary between the agranular–periallocortical* (lap) *and the dysgranular* (ldg) *insula. The white precipitate is the AChE reaction product. This photomicrograph shows how closely the AChE distribution follows architectonic boundaries [26]. In most cortical areas, the amount of AChE closely reflects the amount of choline acetyltransferase and can therefore be used as a marker for regional cholinergic innervation.* (SF = *sylvian fissure.) (×12 before 18% reduction.)*

Discussion

Only cholinergic neurons and their processes contain ChAT. This enzyme is therefore a specific marker for the presynaptic component of cholinergic pathways. Our observations agree with those of previous reports that have demonstrated a rich cholinergic innervation within core limbic structures such as the amygdala and hippocampus [36, 42]. Moreover, the Table shows that the regional distribution of cholinergic innervation within the other parts of the cortical surface is not uniform and that it displays more than sevenfold differences from one area to another. Some of these regional variations are in keeping with those that have been reported by Lehmann and associates [18]. In general the association areas of prefrontal, posterior parietal, and occipitotemporal cortex contained among the lowest levels of cholinergic markers, whereas the paralimbic (mesocortical) areas in the parahippocampal, insular, temporopolar, and caudal orbitofrontal regions had the highest levels. Within these paralimbic areas, the more primitive nonisocortical zones that abut on allocortex tended to have a higher cholinergic innervation than the immediately adjacent but more differentiated isocortical zones. As a group, the primary sensory and motor areas had ChAT levels that tended to be intermediate between the association and paralimbic areas. These results show that cortical cholinergic innervation displays marked and systematic regional variations that parallel the functional and cytoarchitectonic subdivisions of the cortical surface. Especially within paralimbic areas, the changes in cholinergic innervation appear to be exquisitely sensitive to cortical architecture, so a subtle change from an agranular to a dysgranular type of cortex a few millimeters away may be associated with major differences in cholinergic markers (Fig 2). Close attention to architectonic demarcations is therefore advisable in experiments that aim to establish alterations of cholinergic innervation among different groups of subjects or between the two sides of the brain. The cingulate gyrus, which is a major component of the paralimbic belt, appears to be set apart by its relatively low level of cholinergic innervation.

Most of the hippocampal cholinergic innervation in the monkey brain arises from the medial septal (the Ch1 cell group) and the diagonal band (Ch2) nuclei [25]. In contrast, the cholinergic innervation to the rest of the cortical surface as well as to the amygdala arises mostly from the nucleus basalis (Ch4) of the substantia innominata [25]. It is not known if the paralimbic regions receive input from a larger number of nucleus basalis neurons or if cholinergic fibers in these areas simply have more ramifications and a higher ChAT content than in association cortex. The paralimbic areas that have the high cholinergic innervation also send much more extensive projections back into the nucleus basalis and therefore play a more prominent role in the feedback regulation of corticopetal cholinergic pathways [24].

These observations, based on the regional variations of ChAT activity, closely parallel the conclusions derived from anatomical studies based on AChE histochemistry [27]. Unlike ChAT, AChE is not a specific marker of cholinergic neurons. In addition to cholinergic neurons and their processes, AChE is also found within postsynaptic cholinoceptive neurons, where it serves to hydrolyze acetylcholine. Furthermore, noncholinergic cell bodies in the hypothalamus, substantia nigra, nucleus locus ceruleus, and brainstem raphe also contain high AChE levels. As these cell groups also project directly to the cortical surface, they could contribute to the cortical AChE content [26]. However, the high correlations between the regional activities of cortical ChAT and AChE (r = 0.97 in Case 1 and 0.89

in Case 2, $p < 0.001$ in each) suggest either that the AChE from the noncholinergic neuronal groups has a cortical distribution similar to that of the cholinergic innervation or that its contribution to total cortical AChE is modest at best. These considerations indicate that cortical AChE is a reasonably good index of ChAT activity and, therefore, of cholinergic innervation. Fonnum [11] also demonstrated a close correlation between AChE and ChAT activity within subsectors of the hippocampal formation. However, the close correspondence between these two enzymes does not hold everywhere in the brain. For example, the Table shows that the cerebellum contains relatively high AChE levels despite a very low ChAT-specific activity. This discrepancy between cerebellar ChAT and AChE has been shown in several other species [14].

The Table also shows major interanimal differences in ChAT activity. For example, the mean activity for the 33 cortical regions was 6.192 ± 1.020 for Case 1 but 12.905 ± 1.695 for Case 2. In contrast, the mean AChE activities did not show substantial differences (1.317 ± 0.179 in Case 1 versus 1.357 ± 0.234 in Case 2). Despite these interanimal differences, the interareal ChAT variations were very similar in the two cases, as shown by the correlation of 0.88 ($p < 0.001$) between the two sets of 33 cortical areas. Interanimal variations of cholinergic enzymes have been shown in mice [9]. These experiments also demonstrated that mice with higher levels of cholinergic markers performed better in learning tasks. It is conceivable that there are substantial individual variations in the quantity of cortical cholinergic innervation in primates, including humans, and that these variations reflect individual differences in learning abilities.

Research on cortical connections has described several multisynaptic pathways for the transfer of neural information from modality-specific association areas into core limbic structures such as the amygdala and hippocampus [21, 29, 38]. Figure 3 indicates that this sensory information is likely to come under progressively greater cholinergic influences as it approaches the core limbic structures. Moreover, the paralimbic areas that provide a neural matrix for widespread sensory–limbic interactions also contain a particularly rich cholinergic innervation. This anatomical distribution suggests that cortical cholinergic synapses are in a position to regulate the access of sensory information into the limbic system. It is also known that the activity of the nucleus basalis and of its cortical projections is strongly influenced by the behavioral relevance of a sensory event [7, 34]. Cortical cholinergic pathways could thus provide a mechanism for gating sensory–limbic interactions according to the motivational relevance of the ongoing experience. With respect to memory, sensory–limbic interactions are considered essential for the processes of storage and retrieval. Indeed, many

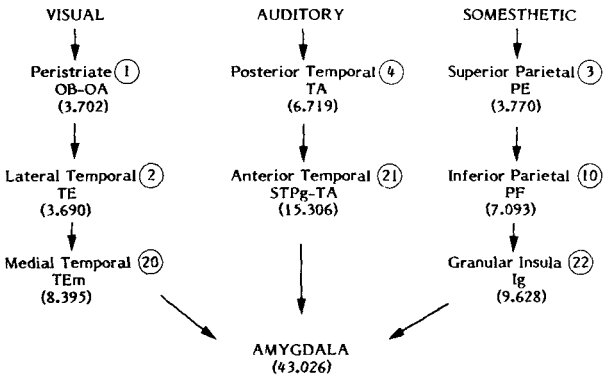

Fig 3. The amygdalopetal flow of sensory information across cortical association areas in the three major modalities. The circled numbers correspond to sample numbers as given in the Table and Figure 1. The numbers in parentheses show the mean choline acetyltransferase activity for that area in the two animals. The architectonic designations are as in the Table. The anatomical evidence for these pathways is discussed elsewhere [21, 29, 39]. This type of analysis was first carried out on endogenous opiate receptors that showed an analogous pattern of distribution [19].

memory disturbances arise as a consequence of lesions that produce sensory–limbic disconnections [13, 21, 29]. The widely recognized contribution of central cholinergic pathways to memory could therefore reflect, at least in part, their role in regulating the transfer of information between sensory association cortex and the limbic system.

The contemporary literature on Alzheimer's disease has placed a great deal of emphasis on the loss of nucleus basalis neurons and on the associated depletion of cortical cholinergic innervation. The suggestion has even been made that the involvement of cholinergic pathways could represent a pivotal component for the entire disease process. As regional variations are known to exist in the distribution of the plaques and tangles in Alzheimer's disease, a pertinent question is whether the degree of cholinergic innervation in a cortical area influences the evolution of these pathological changes. The density of plaques and tangles tends to be highest within the limbic–paralimbic areas and the prefrontal–temporoparietal association regions, whereas it is usually the lowest within primary sensory areas [16]. If the distribution of ChAT shown in Figure 1 is also present in the human brain, it will be necessary to conclude that the level of cortical cholinergic innervation does not play an essential role in determining the regional vulnerability to the formation of plaques and tangles.

Additional cortical transmitters (e.g., norepinephrine, serotonin, somatostatin) are also depleted in Alzheimer's disease [13a, 30]. Furthermore, some cholinergic neurons (e.g., those in the striatum) appear to be spared while many noncholinergic neurons

(e.g., those in cortex, the nucleus locus ceruleus, and the brainstem raphe) show extensive degenerative changes. It appears, therefore, that the distribution of the lesions in Alzheimer's disease is determined by a marker which, if unitary, is unlikely to be cholinergic and that the cell loss in the nucleus basalis represents either an independent component of a multicentric disease or perhaps secondary degeneration caused by the cortical pathology. This latter possibility [1, 3], which shifts the emphasis away from the cholinergic system and toward the cortical involvement, is also in keeping with the observation that subcortical noncholinergic neurons that do undergo degeneration, such as those in the brainstem raphe and nucleus locus ceruleus, have widespread cortical projections, whereas cholinergic neurons that tend to be spared, such as those in the striatum, do not project to cortex. Although there is little doubt that cholinergic pathways figure prominently in the organization of complex mental functions and that cortical cholinergic depletion is a major component of Alzheimer's disease, these considerations provide little support for the hypothesis that the cholinergic lesion constitutes a pivotal prime mover in the pathogenesis of this highly complex disease.

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