Ventromedial Temporal Lobe Anatomy, With Comments on Alzheimer's Disease and Temporal Injury

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The ventromedial temporal area has a complicated topography and neuroanatomy that has yielded secrets only grudgingly. The major features of surface topography are reviewed here as well as recent neuroanatomical findings that establish the ventromedial temporal area as both a recipient of cortical input and the origin for widespread output back to the cortex. The devastating involvement of all ventromedial temporal areas in Alzheimer's disease is highlighted, and comments are offered on the tentorium cerebelli and on mechanical injury to the area.

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This article reviews the complex surface topography of the ventromedial temporal lobe and recent findings on its cortical connections. The involvement of the ventromedial temporal area has profound effects in Alzheimer's disease, and these, as well as the effects of injury to this area, are also discussed.

TOPOGRAPHY OF THE VENTROMEDIAL TEMPORAL AREA IN THE HUMAN AND NONHUMAN PRIMATES

Component Structures

The ventromedial temporal area is a complicated and functionally diverse collection of neural structures along the innermost margin of the temporal fossa adjacent to the sphenoid bone and the petrous part of the temporal bone. The various structures are progressive in an evolutionary sense, reaching substantial elaboration in higher primates and humans, but all mammals have at least partial copies of the core elements. The largely subcortical amygdala is a key part of the ventromedial temporal area, along with the rolled and enfolded allocortical areas that form the hippocampal formation. The superficial allocortical and periallocortical areas that cover the amygdala and hippocampal formation form the parahippocampal gyrus, the third

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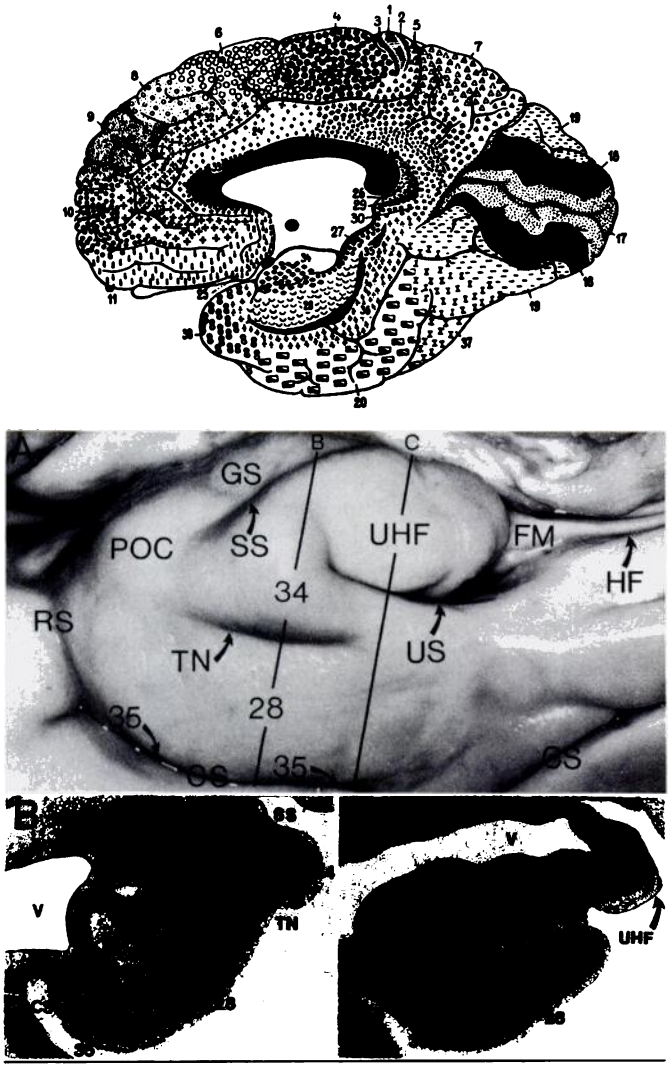
major structure of the ventromedial temporal area. All structures of the ventromedial temporal area are components of the limbic system, and the parahippocampal gyrus is a prominent part of the limbic lobe.[1-7]

Boundaries

The largest part of the parahippocampal gyrus is formed by Brodmann area 28, the entorhinal cortex.[8] Medially and anteriorly, it abuts the primary olfactory and periamygdaloid allocortices; medially and posteriorly, it abuts the subicular allocortices of the hippocampal formation (Figure 1A, B). Posteriorly, the entorhinal cortex nearly reaches the anteriormost part of the lingual gyrus of the occipital lobe in the vicinity of the anterior tip of the calcarine fissure. The lateral borders of the entorhinal cortex, throughout its anterior-posterior extent, is the perirhinal cortex, or Brodmann area 35. This cortex forms a major part of the medial wall of the collateral fissure and intervenes between the highly atypical entorhinal periallocortex and the inferior temporal isocortex, or Brodmann area 36.[9] In lower mammals, the perirhinal cortex may be as narrow as a few cell diameters, whereas in humans it is a sizable (but poorly understood) area.[10,11]

FIGURE 1. **The human ventromedial temporal area in the gross brain (A) and in cross-section (B and C) with Nissl staining. Brodmann's medial view of the human brain is reproduced at the top for comparison. AMG = amygdala; CS = collateral sulcus; DG = dentate gyrus; FM = fimbria; GS = semilunar gyrus; HF = hippocampal fissure; HP = hippocampal formation; POC = primary olfactory cortex; RS = rhinal sulcus; SS = sulcus semianularis; SUB = subiculum; TN = tentorial notch; UHF = uncal hippocampal formation; US = uncal sulcus; V = inferior horn of lateral ventricle.**



Sulcal Landmarks

The only major sulcal landmark of the ventromedial temporal area in humans is the collateral sulcus, which approximates the lateral boundary of the parahippocampal gyrus (Figure 1A, B). Its posterior stem in the occipitotemporal area is nearly invariant from brain to brain, but its anterior parts vary enormously. Unlike the brains of monkeys and great apes, the human brain usually lacks a clear-cut rhinal sulcus.[11] Ironically, this staple of nearly all mammalian brains is nearly absent in the human brain, although our species has a very elaborate entorhinal cortex. If present to any degree, the rhinal sulcus is typically short and/or shallow, resembling a groove more than a fissure or sulcus. Thus, the human entorhinal cortex cannot be viewed as lying "within" the rhinal sulcus as the term would imply and necessitate. Monkeys lack a collateral sulcus and have instead a relatively invariant occipitotemporal sulcus. This entraps a portion of the medial occipitotemporal area into a posterior parahippocampal area posterior to the entorhinal cortex.

Surface Features

Surface bumps and elevations are a prominent feature of the parahippocampal gyrus. They were identified and named near the turn of the century by the Swedish neuroanatomist Retzius.[1] Most conspicuous is the uncus or uncal hippocampal formation. An uncal sulcus, created by the abrupt, hairpin-like medial and upward turn of the anteriormost tip of the hippocampal formation, is an invariant feature of the ventromedial temporal area. Another prominent elevation is the semilunar gyrus, which defines the location of the cortical amygdaloid nuclei.[2,5,7]

Nearly as conspicuous as the uncus, but a few millimeters anterior to it, is the gyrus ambiens, formed by Brodmann area 34 (Figure 1A, B). This is an elevation of

medial entorhinal cortex that occupies a position medial to the point where the free edge of the tentorium cerebelli grooves the entorhinal cortex before it attaches to the clinoid process. Thus, the gyrus ambiens lies directly in the tentorial aperture and bulges into the space of Bichat and the transverse cerebral fissure. In the gross brain, and in cross-sections of scans and stained tissue, the gyrus ambiens is often misidentified as uncus, although the two are decidedly different structures. The former is entorhinal cortex medial to the tentorial notch, and the latter consists of subicular and hippocampal formation pyramids forced out of hippocampal fissure. The gyrus ambiens is always a few millimeters anterior to the uncus and in a cross-sectional or coronal plane through the posterior amygdala.[7] As discussed later, it is the gyrus ambiens or medial entorhinal cortex that leads herniation of the temporal lobe through the tentorial aperture and that is vulnerable to injury when the brain is forced onto the free edge of the tentorium cerebelli.

A conspicuous topographic feature of the ventromedial temporal area in the human brain is the presence of small wart-like bumps on the surface of the entorhinal cortex. These are visible to the naked eye in both fixed and unfixed specimens. Early neuroanatomists named these *verrucae* to call attention to their resemblance to an epidermal disease of viral origin, and Retzius noted their resemblance to the skin of certain amphibians.[1,2] Verrucae are present in apes and monkeys but are far less notable than in humans, where they cover nearly the entire entorhinal cortex, including its medial parts that form the gyrus ambiens. Histochemical studies have shown that the elevations correspond to modules rich in cytochrome oxidase.[12] From a cellular viewpoint they correlate with the islands of large hyperchromatic multipolar neurons that form layer II of the entorhinal cortex.[12,13] These neurons project powerfully to the hippocampal formation, linking the latter to the cerebral cortex via the perforant pathway.[3] The surface features, cytoarchitecture, and connections of the entorhinal cortex set it apart from all other cortical fields in the hemisphere.

CORTICAL CONNECTIONS OF VENTROMEDIAL TEMPORAL AREA STRUCTURES

Cortical Input

Basic facts about the subcortical projections of ventromedial temporal structures were established early in the century by the use of passive staining methodology and dissection. However, studies using these tools were limited in scope and centered largely on compact bundles like the stria terminalis as an output pathway of the amygdala and the fornix as an output pathway of the hippocampal formation. Ramon y Cajal's detailed Golgi studies established many intrinsic connections within the latter and produced the key observation that the entorhinal cortex of the parahippocampal gyrus projects powerfully to the hippocampal formations via what he labeled the *temporo-ammonic* or *perforant* pathway.[10]

Aside from these observations, it was not until the middle of the century, with the advent of experimental neuroanatomical methodology, that a steady flow of new information became available on ventromedial temporal neuroanatomy, and particularly on the degree and nature of cortical connections that link these structures to the remainder of the hemisphere. Especially noteworthy were two classic reports that took on the challenge of describing all of the major corticocortical connections of the rhesus monkey. For each of these reports, the question of where sensory-related cortices project was central, and the skeleton for all cortical association systems was described.[14,15] A finding common to both of these investigations, and many more that have followed,[16–19] is that one of the targets, or end stations, for multisynaptic cortical sensory association systems is the ventromedial temporal area, and cortical input is the major afferent for the amygdala, hippocampal formation, and parahippocampal gyrus. Thus, the ventromedial temporal area receives cortical input not only from the limbic cortices, but also from the association cortices related to the visual, auditory, and somatic modalities. Along with olfactory input from the primary olfactory cortex and visceral input from the insular cortices, the sum total of their cortical input must be viewed as distinctly multimodal.[3] Collectively, these projections have been labeled *feedforward* systems, denoting their sequential stepwise nature and the manner in which sensory information is disseminated within the cortex.[20–22]

The cortical systems discussed above, although large in size, are by no means diffuse with respect to their ventromedial temporal area targets. For example, corticoamygdaloid projections selectively target only certain amygdaloid nuclei,[23–25] and in some cases only parts of them (Figure 2). The lateral amygdaloid nucleus receives at least three cortical projections from the temporal association cortices, and they appear segregated with regard to function. For example, the visual association cortices of the inferior and middle temporal gyri send projections that target the more lateral shell of lateral amygdaloid nucleus and end in a dorsal location. The superior temporal auditory association cortices, in contrast, send axons that end laterally, but ventral to

those from the visual association cortices. The more multimodal temporal polar cortex sends corticoamygdaloid axons that end in the more medial parts of the lateral nucleus. In parts of the lateral amygdaloid nucleus, convergence from more than one sensory modality occurs, with putative taste and olfactory association cortical input contributed by the anterior insular, opercular, and posterior orbitofrontal cortices. Although many details remain unknown, it seems fair to state that the amygdala receives powerful input from the association and limbic cortices of the temporal lobe, anterior insula, posterior orbitofrontal, medial frontal, and anterior cingulate cortices. Many of the systems are organized discretely and target only selective nuclei, or parts thereof, in the amygdala.[24]

Direct cortical association input to the hippocampal formation is far less sizable than that to the amygdala, since it relays first in the perirhinal and entorhinal cortices (Figure 3).[3,26] However, the indirect nature of the anatomy is deceptive. The entorhinal cortex output to the hippocampal formation forms one of the larger cortical association pathways of the cortex, and certainly the largest in the temporal lobe. Collectively, it is known as the *perforant pathway* because its axons pass through or perforate the subicular cortices en route to synaptic sites on the distal parts of hippocampal and subicular apical dendrites and outer two-thirds of dentate gyrus granule cell dendrites (Figure 4). Discrete entorhinal layers provide origin for the perforant pathway.[26,27] For example, layer III projects largely to the subiculum and hippocampal pyramids, whereas layer II contributes the entorhinal-dentate component of the perforant pathway (Figure 5). In the dentate gyrus, perforant pathway axons target approximately 80% to 85% of the postsynaptic space and have a powerful excitatory influence on these neurons. In all mammals investigated, and especially primates, perforant pathway entorhinal cortex axons destined for the hippocampal formation form a compact bundle known as the *angular bundle*, located typically just inside the medialmost part of parahippo-

FIGURE 2. **Darkfield photomicrograph of a cross-section through the amygdala (AMG) of a rhesus monkey after injection of tritiated amino acids in the temporal association cortex, showing terminal axonal labeling *(white)* over various amygdaloid nuclei after autoradiography. ab = accessory basal nucleus; AC = anterior commissure; ce = central nucleus; ct = cortical nuclei; lb = laterobasal nucleus; lt = lateral nucleus; mb = mediobasal nucleus; me = medial nucleus; OC = optic chiasm; RS = rhinal sulcus; SI = substantia innominata; TMAS = temporalis medialis anterior sulcus.**

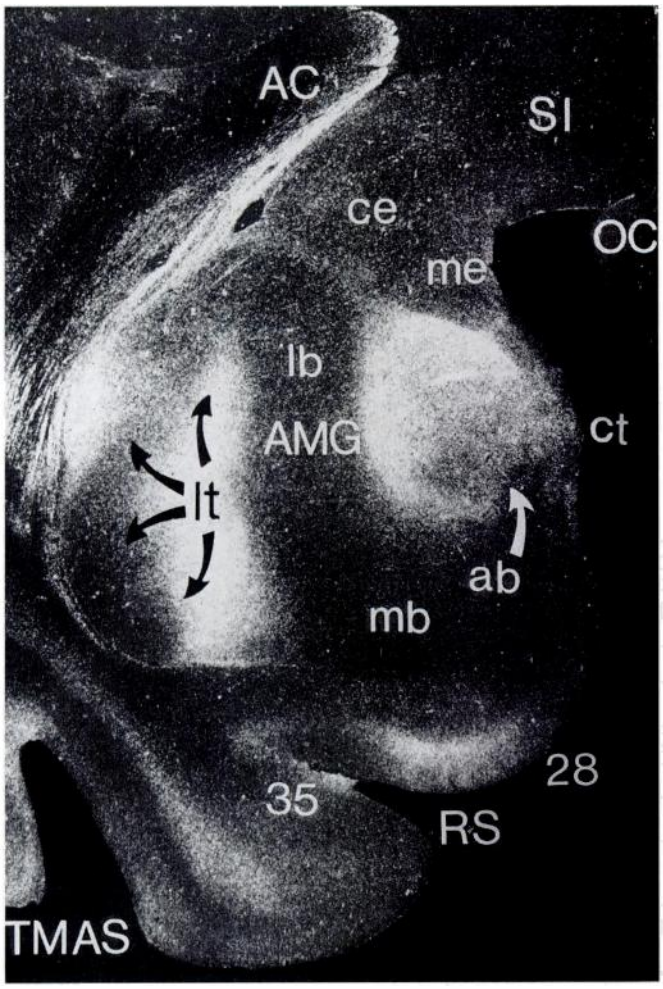


FIGURE 3. **Darkfield photomicrograph of a cross-section through the entorhinal cortex (area 28) of a rhesus monkey after injection of tritiated amino acids in the posterior parahippocampal area, showing terminal axon labeling *(white)* over entorhinal cortex layers I-III after autoradiography. AMG = amygdala; LD = lamina dissecans; RS = rhinal sulcus.**

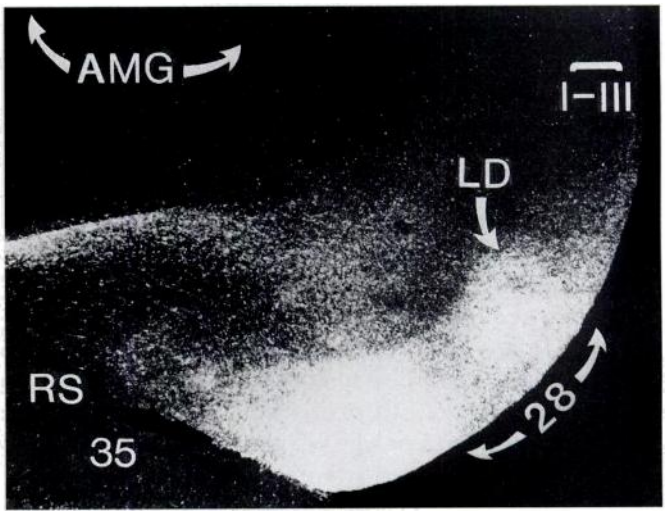


FIGURE 4. Darkfield photomicrograph of a cross-section through the hippocampal formation of a rhesus monkey after injection of tritiated amino acids in the entorhinal cortex and autoradiography showing terminal axon labeling *(white)* along the perforant pathway (PP) terminal zone. FM = fimbria/fornix; ITG = inferior temporal gyrus; LGN = lateral geniculate nucleus; MTG = middle temporal gyrus; PHG = parahippocampal gyrus; PSUB = presubiculum; SG = stratum granulosum of dentate gyrus; SP = stratum pyramidale of hippocampus; ST = stria terminalis; STG = superior temporal gyrus; SUB = subiculum; TC = tail of caudate nucleus; V = lateral ventricle.

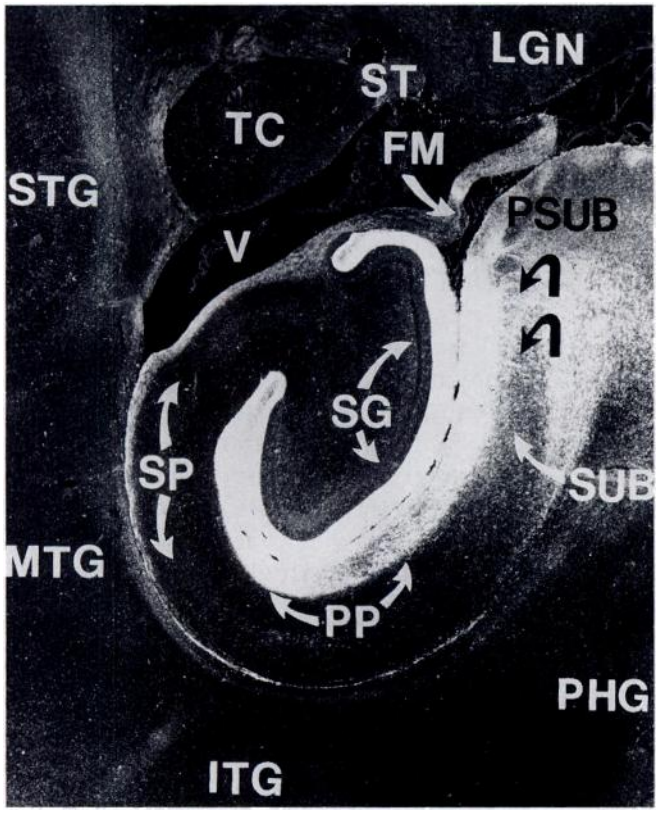
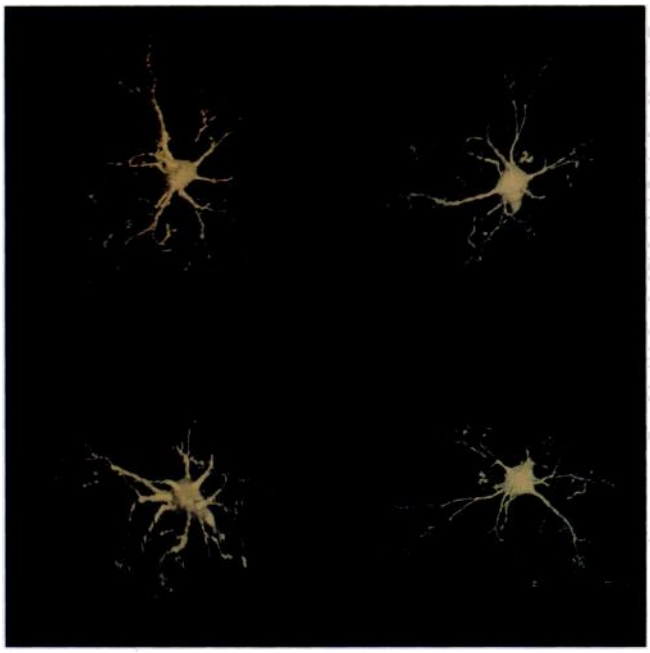


FIGURE 5. A Lucifer yellow–filled layer II multipolar neuron from the rhesus monkey rotated in various planes. The neurons give rise to the entorhinal–dentate gyrus part of the perforant pathway.



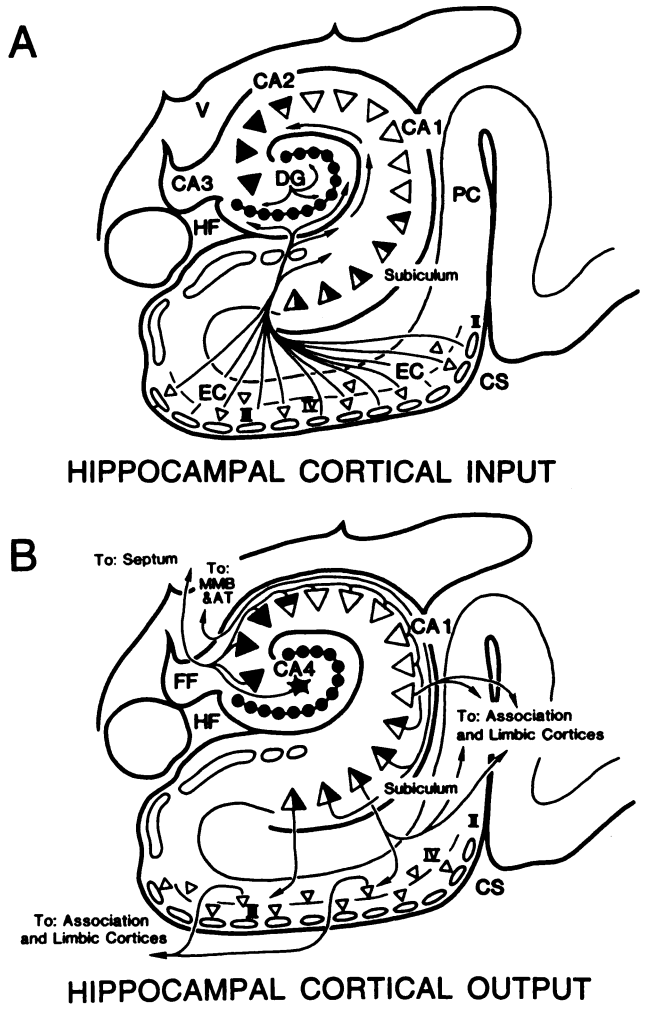
campal white matter adjacent to the ependymal lining of the unopened portion of the inferior horn of the lateral ventricle. Perforating axon bundles leave the angular bundle throughout the anterior-posterior extent of the hippocampal formation.[27] This arrangement is necessary because in nearly all mammals the entorhinal cortex is not entirely adjacent to the hippocampal formation. In fact, in primates much of the entorhinal cortex is located decidedly anterior to the hippocampal formation.

Cortical Output

Although the older neuroanatomical literature stresses the subcortical projections of the ventromedial temporal structures, newer experimental findings reveal substantial feedback projections to the cortex. The amygdala is particularly impressive in this regard and is now known to send axons to the limbic cortex, association cortex, and in some cases even the primary sensory cortex.[25,28] Some of its output to the cortex of the cingulate sulcus is in a position to influence the cells of origin of corticospinal axons that form part of the cingulate motor cortex. Although some of these cortical axons reciprocate corticoamygdaloid projections, it is clear that many do not. Via subcortical projections to the hypothalamus and parasympathetic centers in the brainstem, the amygdala can influence endocrine and autonomic effectors. Via cortical projections, it can influence somatic effector–related motor areas as well as widespread parts of the limbic, association, and even primary sensory cortices. These outputs suggest a greatly expanded role for the amygdala in diverse behaviors located along much of the neuraxis.

The hippocampal formation also is now known to have extensive feedback projections to the cerebral cortex.[3,26,29,30] These arise directly and selectively from the subicular and CA1 pyramids whose axons end in much of the cortex of the limbic lobe and the orbitofrontal, medial frontal, anterior temporal, and posterior temporal association cortices. A powerful contingent of hippocampal cortical output is directed toward the entorhinal cortex, particularly its deeper layers.[29] This output partially reciprocates the strong entorhino-hippocampal projection carried by the perforant pathway (Figure 6A,

FIGURE 6. A: direct cortical input to hippocampal pyramidal neurons (CA1–3) and dentate gyrus granule cells (DG) via the perforant pathway that arises from the entorhinal cortex (EC). B: hippocampal cortical output to the association and limbic cortices from the hippocampal pyramidal neurons (CA1), subiculum, and layer IV of the entorhinal cortex. AT = anterior thalamus; CS = collateral sulcus; FF = fimbria-fornix; HF = hippocampal fissure; MMB = mammillary bodies; PC = perirhinal cortex.



B). However, the latter arises from the more superficial layers of the entorhinal cortex. Thus, intrinsic cortical axons linking entorhinal layers together complete the reciprocity. Nevertheless, layer IV of the entorhinal cortex, which is the target of subicular and CA1 projections, projects widely to many parts of the limbic cortices and to cortical association areas in the temporal lobe. Together, these direct and indirect hippocampal-cortical projections form strong neural systems disseminating hippocampal output.

In summary, ventromedial temporal structures are now known to be a major target of cortical association feedforward axons, and these form their largest input. The cortical areas in question are the so-called distal association areas, meaning they are several synapses removed from the primary sensory cortices. Some are multimodal association areas, but others retain modality specificity. Functional studies of all types link these cortical areas to higher order processes, including memory. The ventromedial temporal structures reciprocate many of their inputs with feedback axons to the association cortices. However, they are unique in being a source of *non*-reciprocal axons to the early association cortices and even some primary sensory areas. This nonreciprocal projection suggests that ventromedial temporal structures can alter initial sensory processing in the cortex and/or can retroactivate or select percepts unique to, or stored in, early association cortical areas.[31–33]

VENTROMEDIAL TEMPORAL AREAS AND ALZHEIMER'S DISEASE

Hippocampal Formation

It has been known for many years that the ventromedial temporal area contains numerous sites of prediction for the pathological alterations that characterize Alzheimer's disease. The hippocampus has received the greatest attention in this respect, and changes in this structure are nearly an invariant feature of the illness.[34] In terms of neurofibrillary tangles, these intracellular alterations occur with greatest frequency in the subiculum and CA1 parts of the hippocampal formation and are less frequently observed in the CA3 and CA4 parts of the structure. Likewise, the granule cells of the dentate gyrus occasionally contain neurofibrillary tangles but frequently are spared entirely. Neuritic plaques, the second signature change of Alzheimer's disease, have a variable distribution in the hippocampal formation, and when present are most conspicuous in the subiculum and CA1 fields of the structure. Here they are invariably scattered among the pyramidal neurons that form the structures and in the molecular layer through which their apical dendrites and terminal dendritic branches course.[35,36] Although neurofibrillary tangles are less frequent in the granule cells of the dentate gyrus, neuritic plaques are commonly seen in the molecular layer of this structure, typically midway between the granule cell soma and the hippocampal fissure. In the subiculum and CA1 zones neuritic plaques are most abundant at the point where the large radial apical dendrites begin dividing into numerous smaller, terminal secondary and tertiary branches. Curiously, in both the dentate gyrus and the hippocampus neuritic plaques occupy the parts of their respective molecular layers where the

largest numbers of terminal axons of the perforant pathway end.[37] Although the hippocampal formation must be regarded as a structure targeted heavily in Alzheimer's disease, it is clear that the distribution of pathology is highly selective, affecting some neurons and not others. No clues exist at this time to explain this selectivity, and hypotheses are equally scarce.

Amygdala

The amygdala is also targeted heavily with pathology in Alzheimer's disease, but only in recent years has its involvement come into sharper perspective.[38,39] Recent studies have focused largely on the presence or absence of pathology in the various subnuclei that form this large and complex structure. Although all amygdaloid subnuclei contain some neurofibrillary tangles and neuritic plaques, a distinct hierarchy exists. For example, the accessory basal, cortical, and mediobasal nuclei all contain large quantities of neurofibrillary tangles and neuritic plaques. The same can be said for the cortical transition area that connects the posteriormost part of the amygdala with the subiculum of the uncal hippocampal formation. In contrast, the medial, central, lateral, and laterobasal nuclei contain less pathology. In fact, the medial and lateral nuclei are very lightly affected, with only occasional evidence of pathology.[38]

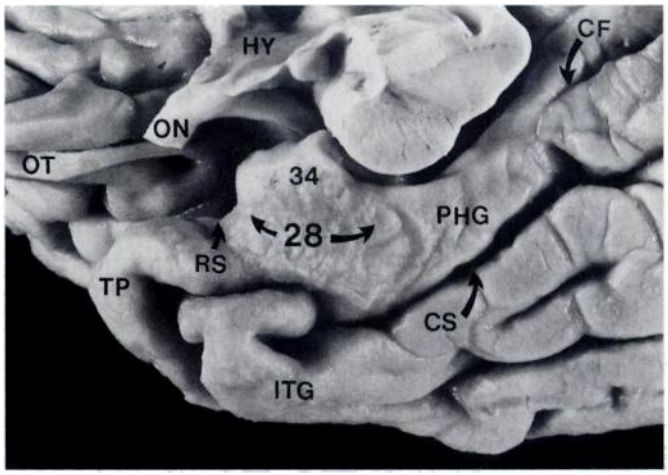
The patterns of pathology in the amygdala in Alzheimer's disease are difficult to categorize in either neuroanatomical or functional terms. For example, the accessory basal, laterobasal, and lateral nuclei all have strong input from and project back to the cortex. However, in Alzheimer's disease only the accessory basal nucleus shows substantial pathology. Similarly, the medial and cortical nuclei both receive olfactory bulb input, yet only the latter is targeted heavily in the disease. Even in a phylogenetic sense, correlations are sparse. For example, the more conservative cortical nucleus is damaged heavily, but its partners, the medial and central nuclei, are not. The more progressive lateral nucleus is largely unaffected, but another component of the newer laterobasal complex, the accessory basal nucleus, is nearly destroyed in a high percentage of Alzheimer's disease cases. At this time, the most noteworthy correlation occurs between amygdaloid nuclei connected to the subiculum and CA1 zones of the hippocampal formation. These would include the cortical transition area and the mediobasal and accessory basal nuclei. All receive hippocampal formation afferents, and all contain abundant pathology in Alzheimer's disease.

Parahippocampal Gyrus

There is general agreement that the parahippocampal gyrus is the most heavily damaged part of the cerebral cortex in Alzheimer's disease and the likely focus for the initial appearance of neurofibrillary tangles.[8,9,35,40] The cortical areas in question form Brodmann areas 28 and 35. Changes in these cortical areas are conspicuous even in the gross brain,[41,42] where the cortex of the parahippocampal gyrus appears atrophic, pitted, and discolored (Figure 7). A distinct laminar specificity of pathology is observed in Nissl-stained preparations and with pathological stains for neurofibrillary tangles. For example, in the early stages of the disease, layer II contains abundant neurofibrillary tangles, and many of the large multipolar neurons contain this alteration. As the duration of illness progresses, layer III will contain neurofibrillary tangles, followed by layer IV. Layers V and VI appear to be the most resistant to this form of pathology, but they likewise may be affected at end-stage Alzheimer's disease and with a long duration of illness. A recent report[43] indicates that 90% of layer II neurons can be lost during the course of Alzheimer's disease and that as many as 58% of all entorhinal cortical neurons are lost. These changes devastate the modular organization of entorhinal cortex seen in the normal human brain and eliminate the characteristic bumps or verrucae that are seen in this cortex (Figures 8 and 9).

Pathological changes in the adjacent perirhinal cortex in Alzheimer's disease are second only to those of the entorhinal cortex, with layers II, III, and V all containing neurofibrillary tangles. In contrast, however, the affected neurons are often seen as distinct columns spanning as many as three layers of cortex.[13] This must be viewed as a modular change as well, but the elements

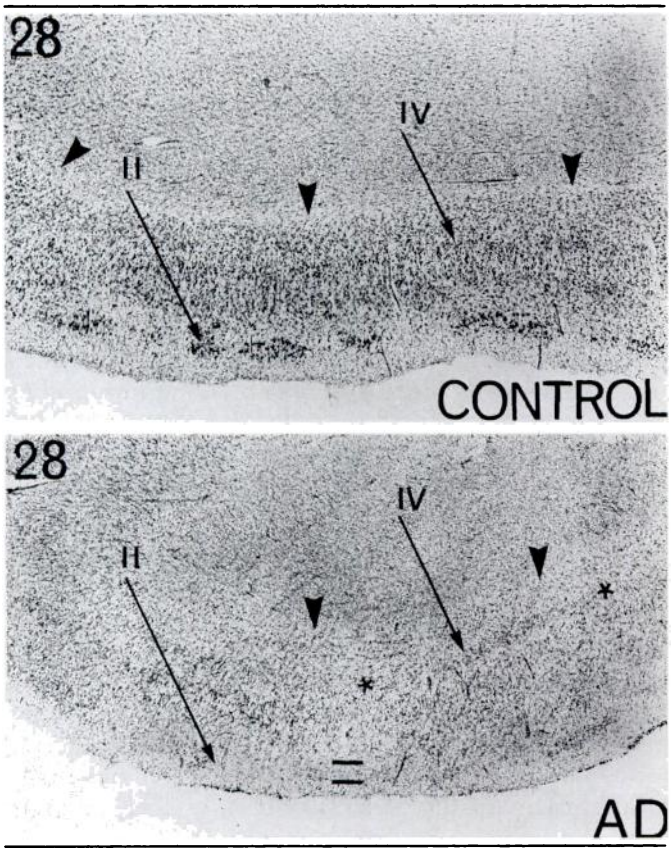
FIGURE 7. **A ventromedial temporal view of the human brain in Alzheimer's disease showing the atrophic and pitted appearance of area 28, the entorhinal cortex. CF = calcarine fissure; CS = collateral sulcus; HY = hypothalamus; ITG = inferior temporal gyrus; ON = optic nerve; OT = olfactory tract; PHG = parahippocampal gyrus; RS = rhinal sulcus; TP = temporal pole.**



and size of modules differ radically between the entorhinal and perirhinal cortices. In the former, the dominant feature of the modularity is the island of layer II neurons and associated pyramidal neurons of layer III. In the perirhinal cortex, the appearance of modules is sharper and is dominated by columns of neurons, with as few as 5 or 6 affected neurons defining the column width.

As discussed earlier, the entorhinal and perirhinal cortices are key cortical areas for linking the hippocampal formation to the cerebral cortex. In fact, they are the essential conduit through which the visual and auditory association areas communicate with the hippocampal formation. The perforant pathway that arises from layers II and III of the entorhinal cortex is the final link in these neural systems. These neurons are heavily invested by neurofibrillary tangles in Alzheimer's disease. However, hippocampal output back to the cortex is also compromised in this disease because the subicular and CA1 neurons of the hippocampal formation are targeted by neurofibrillary tangles and they are the major source of direct-feedback neural systems. Thus, it is arguable that the selective pathological changes in the hippocampal formation and parahippocampal gyrus in Alzheimer's disease virtually isolate this key ventromedial temporal structure from other cortical neural systems (Figure 6A, B).

FIGURE 8. **Nissl-stained cross-sections through the entorhinal cortex (area 28) in a 72-year-old control subject and a 71-year-old Alzheimer's disease (AD) patient, showing the absence of cellular staining in layer II *(crossbars)*. Note that in AD, layer IV is intermittently absent *(asterisks)*. Also note that the normally sharp white matter–gray matter interface *(arrowheads in the control)* is absent in AD because of dense glial cell proliferation.**



VENTROMEDIAL TEMPORAL AREAS AND TEMPORAL INJURY

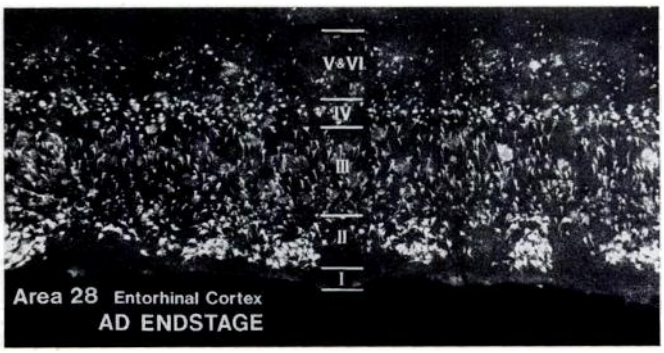
The Tentorium Cerebelli

Although nearly all parts of the ventromedial temporal area are affected by pathology in Alzheimer's disease, other matters related purely to cranial geography jeopardize their integrity. The tight encasement and insertion of the temporal lobe into the irregular bony structure of the temporal fossa creates vulnerability to head injury from direct forces and from forces generated by impact at many points on the skull.[44,45] Likewise, the proximity of the ventromedial temporal area to the inferior horn of the lateral ventricle is also of great consequence with any form of increased intracranial pressure, whether its etiology be tumor, abscess, hematoma, edema, or infarction.[46]

Central to both matters of head trauma and increased intracranial pressure is the fact that the free edge of the tentorium cerebelli cuts across the parahippocampal gyrus before attaching to the petrous apex and the anterior and posterior clinoid processes.[47,48] The collar formed around the brainstem creates an aperture and incisura that provides communication between the supratentorial and infratentorial spaces.

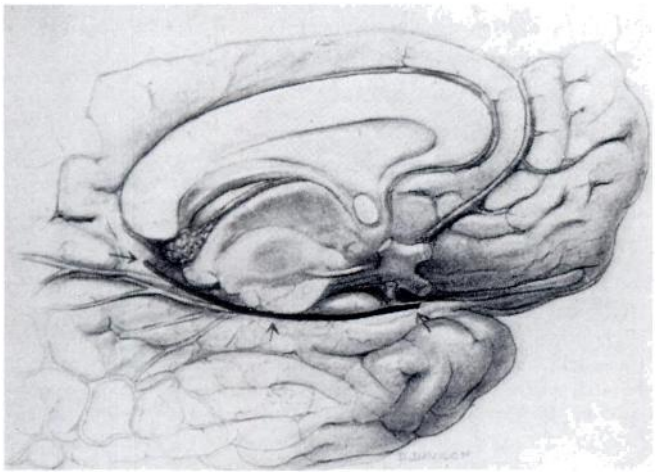
The anterior part of the parahippocampal gyrus sits directly in the tentorial aperture, unprotected by dura

FIGURE 9. **Thioflavine S–stained cross-section through the entorhinal cortex at endstage Alzheimer's disease (AD; 12-year duration of illness), showing dense neurofibrillary tangles in all cortical layers.**



(Figure 10). Although the size of the aperture varies from one individual to another, it has been estimated that the free edge of the tentorium actually contacts and grooves the parahippocampal gyrus in 70% of humans.[49] This tentorial notch or groove ("TN" in Figure 1A) approximates the division between Brodmann areas 28 and 34. Retzius[1] labeled the notch the *inferior rhinal sulcus*, and others have followed his lead. However, in the present author's estimation this indentation is nothing more than a surface marking in some human brains relating purely to the disposition of the free edge of the tentorium cerebelli.

FIGURE 10. **A reproduction of Figure 1 from Jefferson's classic article "The Tentorial Pressure Cone"[48] showing the course and line of contact of the free edge of the tentorium cerebelli across the parahippocampal gyrus of the human brain. The location of the gyrus ambiens component of the entorhinal cortex is shown.**

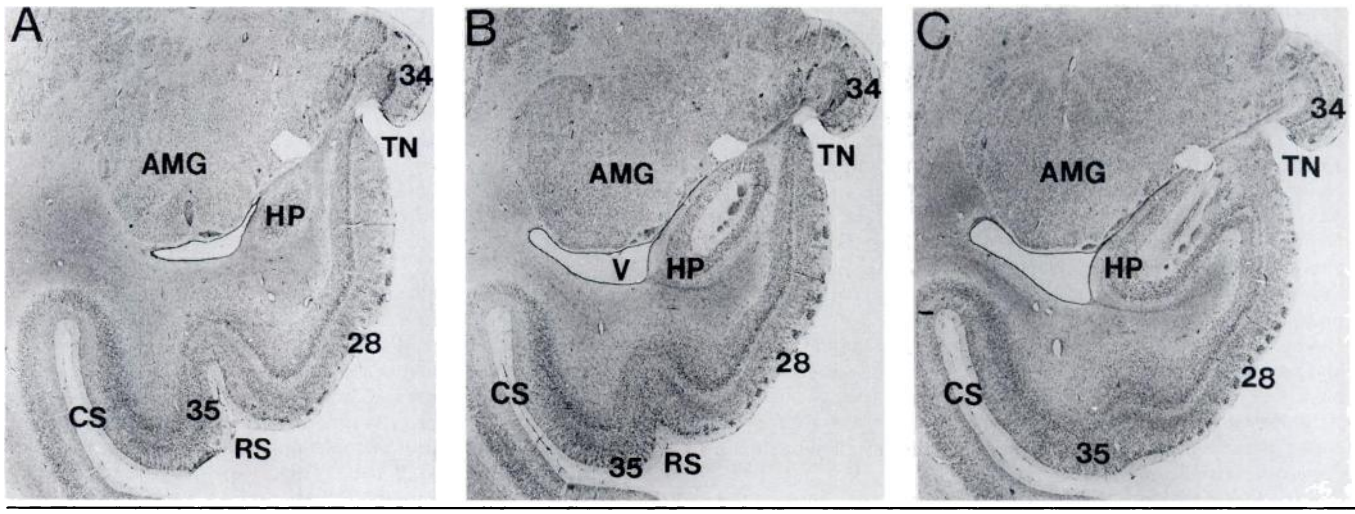


Uncal Herniation With Head Injury and Raised Intracranial Pressure

The location of the tentorial incisura and the complications it creates in neurological disease have been long appreciated. Quite simply, spatial compensation is limited in the supratentorial space, and when it is exhausted, the brain will herniate across the free edge of the tentorium into the space of Bichat and the infratentorial compartment.[45] The results necessitate immediate emergency-related measures to preserve life. *Uncal herniation* is an appropriate term to apply to extreme herniation and to pathological specimens where fatality occurred. However, in technical terms, it is not the uncal hippocampus that lies in the tentorial aperture, but in fact the entorhinal cortex of the anterior parahippocampal gyrus. It, and not the uncus, leads the invasion of infratentorial space. Partial herniations that are not fatal may result in entorhinal injury. Behavioral changes in such patients would be of great interest.[44]

In a related chord, a majority of individuals suffering head trauma survive their injuries. However, in such a population it would be expected that many might have injuries to ventromedial temporal areas around the free edge of the tentorium (Figures 11A–C), since the temporal lobes are often forced onto a part of it around the incisurum. Posttraumatic behavioral changes in head injury survivors, particularly those with emotion-re-

FIGURE 11. **Three Nissl-stained cross-sections of the ventromedial temporal area showing injury along the tentorial notch (TN) by the free edge of the tentorium cerebelli in a 62-year-old patient who suffered from agitated depression and psychoses following a bicycle fall and head injury 19 years prior to death. Note the deep cut at the tentorial notch separating Brodmann areas 28 and 34 and the abnormal elevation of the unherniated hippocampal formation. AMG = amygdala; CS = collateral sulcus; HP = hippocampus; RS = rhinal sulcus; V = lateral ventricle.**



lated and memory-related sequelae, could just as likely be related to ventromedial temporal area injury as to the more obscure causes, such as axon shearing, proposed by some.

CONCLUDING REMARKS

The ventromedial temporal area has long been known to have efferent projections to subcortical structures involved in endocrine and autonomic processes. Less has been known about its connections with the cortex and the manner in which it is related to neural systems operative in memory. The details of a reciprocal interrelationship between ventromedial temporal areas and the remainder of the cortex have been established in the past three decades.[3] A mutually compatible dialogue now exists between anatomy and behavior, and continuing progress and insight have been achieved on both fronts.[50–53]

However, the ventromedial temporal area is involved in a bewildering array of neurological and psychiatric diseases, ranging from Alzheimer's disease to autism[54] and schizophrenia.[40,55] Pathogens such as viruses attack the area, and mechanical injuries around the tentorium cerebelli are well known. Yet the etiologies for many alterations are unknown, and all behavior changes are not clearly in the realm of memory. A foothold has been established with regard to memory, but the four decades that have passed since the studies of the amnestic temporal lobectomy patient H.M. serve only to remind us of the long journey ahead.

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