The Role of the Entorhinal Cortex in Paraphrenia

Manuel F. Casanova

Abstract Evidence derived from postmortem brain studies has implicated the uncal cortex in paraphrenia. In the present review, we expand on the anatomic and physiologic nuances endogenous to this region that make entorhinal cortex pathology an important clinicopathological correlate to paraphrenia. First, we summarize the anatomic landmarks and histologic features that will allow the reader to define the entorhinal region in future research studies. As cortical regions usually project to neighboring cortices, inferences will be drawn as to the function of the entorhinal region based on the surrounding cortical regions. The results will help explain why patients with paraphrenia may exhibit amnestic deficits that stand in contrast to a well-preserved thought process and personality. We also review the results of surgical ablation studies in animals. These studies suggest that some risk factors currently associated with paraphrenia (eg, social isolation) may in reality be an early manifestation of entorhinal pathology. Finally, the author provides a parallelism between the hallucinations observed in some paraphrenic patients and the results of electrical stimulation of the uncal cortex. The results will help explain why hallucinations in paraphrenia are usually limited to the patient's surroundings.

Keywords Paraphrenia · Schizophrenia · Entorhinal cortex · Transentorhinal cortex

M. F. Casanova (✉)
Department of Psychiatry, University of Louisville,
500 South Preston Street, Building A, Room #217,
Louisville, KY 40292, USA
e-mail: manuel.casanova@louisville.edu

Introduction

The entorhinal cortex, or Brodmann's area 28, is located in the ventromedial aspect of the rostral third of the temporal lobe. In its anteriormost portion, the entorhinal cortex expands in apposition to the amygdala, prorhinal, and prepiriform cortex. Caudally, it bridges the intrarhinal sulcus and covers a considerable portion of the parahippocampal gyrus until it gradually fades into a cortex having both iso- and periallocortical attributes (ie, proisocortex). Throughout its major extent, the entorhinal region is flanked on its medial border by the pre- and parasubiculum. In some species, such as the mouse, the subiculum proper slips underneath the pre- and para-subiculum and terminates adjacent to the lower strata of the entorhinal cortex [1].

The lateral aspect of the entorhinal cortex is made by the "transentorhinal cortex" of Braak (perirhinal cortex, or Brodmann's area 35). The transentorhinal cortex marks the flexure at which the parahippocampal gyrus invaginates into the collateral sulcus. It should be noted that conflicting information exists in the literature as to whether the transentorhinal cortex comprises a subdivision of the entorhinal cortex or a separate cortical region [2–4].

Macroscopically, the occasional presence of small elevations surrounded by shallow grooves, the so-called verruca hippocampi, marks the approximate extension of the entorhinal cortex. According to several authors, this region undergoes a remarkable increase in extension and laminar complexity as the phylogenetic scale is ascended [4–6]. In the human brain, for example, Braak [4] considers that the entorhinal region spreads throughout a considerable portion of the parahippocampal gyrus. However, other authors, especially Van Hoesen [7], restrict the entorhinal cortex to the anteriormost portion of this gyrus. According

to Amaral and Insausti [8] the entorhinal cortex of humans first appears 5 mm rostral to the amygdala and terminates just anterior to the lateral geniculate nucleus.

The laminar organization of the entorhinal cortex has given rise to divergent patterns of nomenclature. According to Ramón y Cajal (cited by Amaral et al. [2]), the first description of the structural organization of the entorhinal cortex belongs to Hammarberg [9], who defined this region as a five-layer cortex. His description (including layer thickness, cell size, and packing densities) is beautifully illustrated as part of an atlas comparing the brains of mentally retarded individuals with those of controls. Later, Ramón y Cajal [10] concluded that the entorhinal region or "angular ganglion," as he called it, consisted of seven layers. Relying mostly on the Golgi technique, Lorente de Nó [11] modified that classification by limiting the number of layers to six. The major difference between the two nomenclatures refers to the proper labeling of the lamina dissecans. Other authors have divided the entorhinal cortex into a laminae principalis externa and interna with an interposed lamina dissecans [12, 13]. Their reluctance to use a numbering scheme underlies a perceived impropriety in associating layers of the entorhinal cortex with those of the neocortex [8].

The lamina dissecans is a cell-sparse but fiber-rich region identified by Cajal as the deep plexiform layer and included within the Lorente de Nó [11] classification as layer IIIa. The presence of a space replacing the layer of internal granule cells resembles other "primitive" cortices such as the anterior cingulate gyrus and insula. In these primitive fields, lamina IV is practically devoid of neurons and difficult to identify. In the entorhinal cortex, granule cells are also conspicuously diminished in number, but a space (the lamina dissecans) remains as a tombstone of what should have been their location. A prominent granular cell layer IV usually signifies a strong thalamic input. In the entorhinal cortex, the projections to the cell-sparse layer IV are dominated by afferents from the subiculum [7]. Dopaminergic innervation from the ventral tegmental area also provides a major source of afferents, but these go primarily to layers II and III [14, 15].

Ever since the initial attempts at defining the layers of the entorhinal area, nomenclatures for the proper identification of this region have grown in abundance. Most of the proposed classification schemes bear great resemblance to each other but differ in regard to the ordering sequence. We prefer adherence to the nomenclature of Van Hoesen and Pandya [16] due to its widespread usage and because the alternate nomenclature of Rose [17] was based on an erroneous interpretation of the cortical layering patterns of this region during development. According to the classification of Van Hoesen and Pandya [16], layer I is the most superficial and consists of a cell-sparse region often called

the *plexiform zone*; medium to large stellate cells (modified small pyramidal neurons) comprise layer II; a wide zone of medium pyramidal cells constitutes layer III; layer IV is a lamina dissecans (variably present according to the subdivision of the entorhinal cortex); a thin layer V is composed of small pyramidal and horizontal cells; finally, a striated or multilaminated layer VI features many polymorphous and spindle cells.

At the microscopic level, the entorhinal cortex is not homogeneous and has been subdivided according to a series of cytoarchitectural criteria, including the glomerular or linear arrangement of layers II and III, the width of the acellular gap between layers II and III, the presence or absence of a lamina dissecans, and the pattern of multi-lamination in the deeper layers [2, 18, 19]. (For silver impregnation criteria, see Lorente de Nó [11] and Blackstad [20].) The lack of sharp borders between the different subfields has given rise to divergent interpretations. Thus, Rose [17, 21] and Sgonina [13] described 23 entorhinal subfields in the human brain. Filimonov [22] described 18. Macchi [23] referred to five. Most recently, Braak [12] claimed at least 16 different subfields. The use of modern neuroanatomic techniques that allow the tracing of afferent and efferent connections to a particular region may help clarify this controversy [3].

Connectivity

The entorhinal cortex lies partially in the rostral and ventral portion of the S-shaped infolding of the hippocampal formation. Its major output is through the perforant pathway, which originates in layers II and III [24]. These projections end on the dendritic plexus of the inner third of the molecular layer of the dentate gyrus. Braitenberg and Schüz [1] remarked that the awkward convolution of the hippocampus is an attempt to bring the dentate gyrus in proximity to the entorhinal cortex.

Conceptually, the entorhinal cortex forms part of a paralimbic cortical belt flanked by the allocortex (the three-basic layer cortex) at one extreme and isocortex (the six-layer cortex characteristic of the neopallium) at the other. As the major connections of the entorhinal cortex are with adjacent cortical sites, theoretically, it may bridge information pertaining to its neighboring areas: memory, affective experience, and drive (ie, the limbic system), with extensively processed information related to the extrapersonal space (ie, isocortex). In effect, according to Mesulam [25], the paralimbic formation along with other heteromodal or higher-order association areas accomplish two major transformations of information: "the further associative elaboration of sensory processing and the integration of this information with drive, affect, and other aspects of mental content."

Behavioral studies in surgically lesioned monkeys have corroborated the information-processing capacity of this region. Thus, bilateral lesions of the hippocampus, including the entorhinal cortex, produce substantial memory impairment in monkeys [26, 27], whereas lesions confined to the hippocampal efferent system (eg, fornix), one of its projections sites (eg, mammillary bodies), or the amygdala (but sparing the entorhinal cortex) produce—in the worst-case scenario—transient memory impairment [26, 27]. Similarly, in rodents, lesions of the entorhinal cortex, but not the dorsal hippocampus, provide for disruptions in latent learning tasks [28•].

The entorhinal cortex has few if any connections with primary sensory and motor cortices. This may explain why the information initially derived from the visual, auditory, or somatosensory cortices is not deformed or influenced by the emotional state of the individual [25]. According to the concepts of Jones and Powell [29], which were later extended by Mesulam et al. [30], the sequential flow of sensory information through the brain follows connections from primary sensory cortices to modality-specific association areas and from there to sites of sensory convergence. These polymodal association areas direct their afferents to supramodal cortical sites (eg, the perirhinal [entorhinal] area) [31]. Polymodal association areas projecting to the entorhinal cortex include the prefrontal cortices, rostral insula, and superior temporal sulcus. The entorhinal cortex also receives projections from the amygdaloid complex and its circumfluent olfactory, periamygdaloid, and presubicular cortices. These projections allow the hippocampus to receive multimodal sensory information derived from the external (association cortex) and internal (amygdala) environment.

It is noteworthy that projections to the entorhinal cortex are reciprocated after synapse in the hippocampus. Thus, a major efferent pathway of the hippocampus goes via the subiculum to the entorhinal cortex of the parahippocampal gyrus and ultimately returns to the association cortices. In the entorhinal cortex, the overlap of afferent hippocampal projections with efferent pathways destined for the hippocampus (eg, perforant pathway) provides the angular ganglion with an opportunity to play a pivotal role in modulating information through the limbic system.

The importance of the connectivity pattern related to the transfer of information between the prefrontal cortex and the hippocampus bears some comments. In an early study on the efferent projections of the prefrontal cortex of the monkey, Nauta [32] emphasized the influence of the dorsolateral prefrontal cortex on the hippocampus via its connections to the cingulate gyrus and presubiculum. More recent studies have shown that a major portion of the afferent projections to the entorhinal cortex are derived from the orbital and dorsolateral prefrontal cortex [33]. A

re-evaluation of the Nauta [32] anatomic scheme based on these observations reveals that projections to the entorhinal cortex provide a more direct means for the frontal lobe to influence the hippocampus. Tracing studies in monkeys have shown that these entorhinal to medial-orbital frontal cortex connections are reciprocal [34, 35].

The above-related evidence suggests that lesions of the entorhinal cortex lead to memory impairment without affecting salient personality traits. Memory impairment remains mild until degenerative changes involve other susceptible areas. In a study by Giannakopoulos et al. [36] of 1,200 brains of older adults, hippocampal alterations correlated with age-associated memory impairment, whereas neurofibrillary tangle formations in the neocortical association areas of the temporal lobe were required for development of Alzheimer's disease. The stagnation of neuritic changes in the limbic system in both paraphrenia and neurofibrillary tangle–predominant senile dementia explains the mild amnestic state and preservation of personality traits observed in these conditions.

Physiology

Surgical lesions and electrophysiologic studies have provided another way of looking at the entorhinal cortex. Intracellular recordings in animals have shown that transmission of information through the entorhinal cortex and into the hippocampus proper is modified during different behavioral states (eg, sleeping vs waking) [37]. Dahl and coworkers [38] believe that the purpose of this modification is to adjust the hippocampal function according to the requirements of the prevailing behavioral state. Monoaminergic projections from the brainstem, such as the serotonergic system from the raphe and the noradrenergic system from the locus coeruleus, restrict or modulate the transmission of signals from the entorhinal cortex to the dentate gyrus [38–40]. The integrity of these brainstem projections as well as their terminal fields (eg, entorhinal region) therefore may be necessary to modulate the transmission of incoming stimuli from association and adjacent cortices into the hippocampus. Dysfunction of these systems may underlie the disrupted or fluctuating sensory integrative functions observed in paraphrenia patients.

Similarly intriguing are the data on entorhinal cortex function derived from electrical stimulation of the human brain. Almost half a century ago, Penfield and Perot [41] recorded the experiences of epilepsy patients during electrical stimulation of certain parts of their brains. The images thus elicited were so vivid that they considered them to be memory traces of past experiences. According to this theory, the images elicited would be the enagram that was closest to the stimulating electrode [42, 43]. Most

commonly, patients during stimulation would relate hearing or watching another person's actions and speech. It is intriguing that of all the possible responses, some were seldom elicited. These included experiences in which the patient himself or herself was engaged in speaking, thinking, or performing some skilled behavior [44]. In the Penfield and Perot [41] series, which involved 1,132 awake patients, these responses were rarely observed (only in 8% of the patients), and then only with temporal lobe stimulation. Perceptual experiences were most commonly noted with stimulation of the superior temporal gyrus, planum temporale, uncus (entorhinal cortex), and the brim of the collateral sulcus [41]. The large number of experiential responses derived from the superior temporal convolution as opposed to the few elicited from the parahippocampal gyrus may be an artifact due to the fact that the base of the temporal lobe was stimulated much less often than the lateral surface [41]. A comparison of the responses elicited from the lateral and medial cortex of the temporal lobes found more lasting effects from periamygdaloid stimulation. In contrast to the lateral temporal lobe responses, those stemming from its medial aspect were associated with an after-discharge and behavioral automatisms that endured for 1 min or more after cessation of the current [45].

At present, some investigators consider that the phenomenon described by Penfield and Perot [41] did not reflect the recall of past experiences but instead represented vivid experiences that were dependent on the preexisting personality, cognitive state, and expectation of the patients [46–48]. Thus, in contrast to the theory of localized engrams of Penfield [42], those stimuli capable of eliciting the formation of images were associated with widespread electroencephalographic changes [47]. Similarly, electrical stimulation of widely spaced anatomic sites could produce the same images [49]. Finally, in the surgical experience of most investigators, excision of the area stimulated by the electrode did not remove the memory of the experience [49, 50].

Results of behavioral studies in monkeys after complete amygdalectomy, including removal of the entorhinal cortex, have varied depending on the age, sex, and postoperative testing environment [51, 52]. Surgically operated adult and juvenile male monkeys exhibited a fall through the social hierarchy and a diminution in their aggressive behavior. Occasionally, some of the lesioned monkeys were subjected to an increased number of attacks by normal members. Contrary to these observations, amygdalectomized adult female monkeys occasionally increased their aggressive behavior and rose in social rank. Maternal behavior was never seen in lesioned females; rather, they abused and/or neglected their infants. Operated juveniles presented still a different behavioral conduct consisting of heightened oral and sexual activity, whereas infants with similar lesions displayed a grossly normal interaction with their mothers. It may be worth adding that lesioned infants later (at 2 years to 3 years of age, or roughly at the onset of puberty) exhibited aberrant behavior. The absence of early symptomatology in these brain-injured infants was attributed to the immaturity of the central nervous system and the strong mother–infant bond that can be established despite the lack of reinforcement by the young [51, 52]. After release in their natural environment, amygdalectomized adult animals failed to resocialize and never re-entered their troop. Although tame in a cage situation, when they were free, they did not allow experimenters to recapture them. According to Kling [51, 52], the social drift in these operated animals seems related to entorhinal (uncal) cortex damage, whereas abnormalities in sexual behavior (part of the Klüver-Bucy syndrome) were the result of lesions in the lateral nuclei of the amygdala. Partial ablation of the amygdala with sparing of the uncal cortex decreased aggressive behavior while simultaneously allowing for resocialization, albeit at a lower social rank.

The symptomatology expressed in surgically intervened animals calls into question the veracity of some of the so-called risk factors in paraphrenia. The accepted trend of thought is that paraphrenia patients exhibit a trend toward social isolation as a result of their premorbid personality. However, behavioral studies from ablation studies suggest that these may be early manifestations of uncal pathology.

Pathological Correlations

Although descriptions of entorhinal pathology in paraphrenia have appeared in the literature only recently, the role of the temporal lobe in the pathophysiology of this illness was suggested from previous postmortem studies. Organic processes such as encephalitides, cerebrovascular accidents, tumors, and head injury leading to temporal lobe damage may present with schizophreniform symptoms [53, 54]. Viral infections and cerebral tumors associated with psychotic manifestations tend to involve the limbic structures of the temporal lobes, hypothalamus, or cingulate gyrus [53]. Similarly, a relationship between schizophrenia-like psychosis and epilepsy has been suggested by many researchers [55]. The automatisms and high prevalence of sphenoidal spike activity in this schizophrenic-like psychosis of epilepsy suggested involvement of medial temporal lobe structures [56]. Neuropathological investigations of resected temporal lobes from complex partial seizure patients have shown a wide variety of pathological changes. Usually the amygdala, hippocampus proper, uncus (entorhinal cortex), and the more posterior parahippocampal gyrus are involved [57]. Although gliosis is the most common pathology, both ganglioglioma-type tumors and

heterotopic patches of gray matter often have been noted [58]. Topographical analysis of these abnormalities indicates that the incidence of psychosis is highest for those lesions of presumed developmental origin lying toward the medial aspects of the temporal lobes (ie, the entorhinal cortex) [59]. Not coincidentally, the neuropathology of paraphrenia is characterized by neurofibrillary pathology affecting the entorhinal and transentorhinal cortices, with little in terms of amyloid deposition. The pathology is the major substrate for mild cognitive impairment and memory decline in affected patients [60•].

Conclusions

In summary, this article complements several recent studies suggesting entorhinal cortex pathology in paraphrenia and emphasizes some of the anatomic and physiologic characteristics of the region. We propose that a lesion in the entorhinal cortex may result in "misreading" of information directed to the limbic system. The information thus distorted leads to the intrusion of foreign images and ideas. This possible clinicopathological correlate should not prevent attempts to uncover abnormalities in other anatomic locations. The borders of the entorhinal cortex have been artificially defined to comply with a number of cytoarchitectural criteria. However, the connections of the entorhinal cortex indicate that the functional effects of this area extend well beyond the temporal lobes. It seems possible that in paraphrenia, rather than there being a single locus of pathology, a whole anatomically interlinked system is involved. In this connectivity scheme, the authors emphasize the possible involvement of the entorhinal cortex.

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