The development concept of "endogenous psychoses"

Helmut Beckmann, MD; Hermann Jakob, MD; Dieter Senitz, MD

Several structural deviances in the brain in "endogenous psychoses" have been described over the last decades. The enlargement of the lateral ventricles and the subtle structural deficits in temporobasal and orbital frontal structures (hypofrontality) are reasonably well established in the majority of schizophrenic patients. We examined the cytoarchitecture of these important central structures, namely the entorhinal region and the orbitofrontal cortex (Brodmann area 11), which have been under meticulous investigation in our laboratories over the last few decades. In a new series of schizophrenic patients and normal controls, we made serial cuts of the whole rostral entorhinal cortex on both sides. For this report, we selected two cases with very different psychopathologies, and present the serial cuts through both hemispheres and the malformations found. We report on the differing magnitude of the heterotopic malformations (for definition see page 103), either bilaterally or unilaterally.

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Author affiliations: Clinic and Polyclinic of Psychiatry and Psychotherapy, University of Wuerzburg, Wuerzburg (Helmet Beckmann, MD; Dieter Senitz, MD); Laboratory of Neurobiology, General Hospital of Psychiatric Illnesses, Wiesloch, Germany (Herman Jakob, MD)

Entorhinal region

The entorhinal region is an outstanding, differentiated "association center" within the allocortex.[1] It is intimately connected with the hippocampus by way of the perforant pathway. It thus forms, together with the hippocampus, a multineuronal regulatory circuit at the center of the limbic system. Signals arriving in the entorhinal cortex proceed to the hippocampus, pass through several synapses, and return, in part, to the entorhinal cortex. This regulatory circuit seems to be of major importance for the storage of orientation and also for memory.[2]

Studies in primates have shown that primary cortical fields and all secondary cortical fields with visual, auditory, and somatosensory functions have reciprocal connections with the entorhinal cortex, either directly or by way of the perirhinal area.[3-5] The multisensory areas in caudal portions of the orbitofrontal region, and the rostral and ventral fields of the claustrocortex, project mainly onto the rostral fields of the entorhinal area *(Figure 1)*.[6] Furthermore, as extensive studies in the cat have shown, there are well-developed systems of both longitudinal and transverse connections that enable the activity of systems within the entorhinal cortex to be integrated with the complex of afferent information. Sensory afferent information is delivered to the hippocampus by way of the upper layers of the perirhinal

Address for correspondence: Helmut Beckmann, MD, Department of Psychiatry and Psychotherapy, University of Wuerzburg, Fuechsleinstrasse 15, 97080 Wuerzburg, Germany
(e-mail: Beckmann_h@klinik.uni-wuerzburg.de)

area and the entorhinal cortex. Efferent projections arise from the lower layers of the perirhinal and entorhinal areas. The entorhinal cortex thus integrates information from all sensory modalities from both the interior and the exterior of the organism.[7-10]

The allocortex is roughly divided, on a topographical basis, into medial, lateral, and perirhinal portions. The perirhinal area, which is also called the transentorhinal subregion,[1] lies between the lateral part of the entorhinal cortex and the isocortex of the temporal lobe.[11] It displays the full array of cortical layers in a coronal section passing through the central portion of the amygdala, in the entorhinal central medial and lateral area (and the interpolar medial area); it is most highly differentiated in the central lateral area. The upper portion of the cortex, the principal external lamina, is divided[12] into the zonal lamina (layer I) and the Pre-α (layer II), Pre-β, and Pre-γ (layer III) layers, and the adjacent acellular layer, the lamina dissecans (layer IV). The lower portion of the cortex, the principal internal lamina, is subdivided into the Pri-α, Pri-αβ, and Pri-αγ sublayers (Pri-layers), which consist mainly of pyramidal cells. In the central fields, layer II Pre-α consists mainly of islands of similar-appearing, medium-sized to large multipolar "modified" pyramidal cells with long axons extending into the white matter. This type of neuron is characteristic of this area and is not found elsewhere.[1]

Detailed observations concerning the development of this area were made by way of autoradiographic studies of rhesus monkey embryos at different developmental stages.[13,14]

These findings may be regarded as a model of the developmental process in humans.[15,16] The matrix for archicortical and periarchicortical areas corresponding to the hippocampus and the entorhinal cortex lies in the medial wall of the hemispheric vesicle, the initial embryonic precursor of the cerebral hemisphere. The neuroblasts destined to form the cerebral cortex are already determined at this stage.[17,18] While the neuroblasts of the ventricular zone form the lower layers of what will later become the entorhinal cortex, the subventricular zone gives rise to its upper layers. This is also the site where, after the last cell division, active movement of the neuroblasts (ie, cell migration) begins. Neurons at this stage have a leading process, a fusiform, bipolar shape with an ovoid nucleus, and a long trailing process and are called "young neurons." The leading process is essential for movement of the migrating neuron.[19,20]

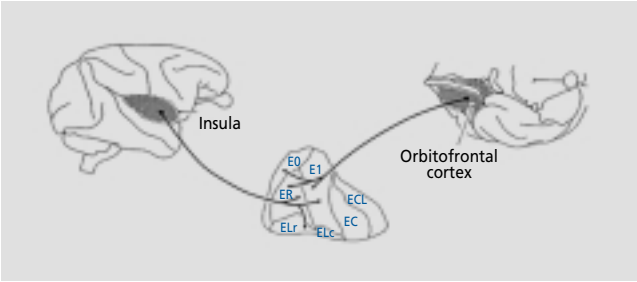

Figure 1. The (mostly cortical) afferent projections of the primate entorhinal area. EO, olfactory field; ER, rostral field; Elr, rostral-lateral field; EI, intermediate field; EC, caudal field; Elc, caudal-lateral field; ECL, caudal limiting field.[6]
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"Cohorts" of closely spaced young neurons migrate along the course of previously laid down glial fibers outward to the cortical plate, passing by groups of neurons that had reached their destination earlier, and proceed to the outermost surface of the cortical plate, thus forming "vertical or ontogenetic columns."[17] The young neurons do not assume their mature pyramidal or polygonal shapes until shortly before they reach their cortical destinations. Later, as further columns migrate to the surface, they become submerged in the deeper layers. This so-called inside-to-outside spatiotemporal gradient is operative for all neocortical and most allocortical areas of the human brain.[15,16]

The development of the entorhinal area in humans is similar to the development in the rhesus monkey described above in many important aspects, although it is not yet known in equivalent detail. Compared with other cortical areas, the entorhinal area develops in a relatively brief period of migration. The earliest evidence of a germinal epithelium, or matrix, in the developing fetus is found in the third month at the base of a caudal area of the lateral ventricle. The first signs of migration are demonstrable in embryos aged approximately 10 weeks.[21] At the end of the third gestational month, entorhinal and presubicular areas can already be distinguished in the cortical plate.[22] Positions in the cortex are occupied in the sixth month, and the matrix is entirely depleted in the seventh.[11] Further details of the early development of the entorhinal cortex in humans remain controversial.

In one study,[23] 78 out of 120 cases of schizophrenia showed major cytoarchitectural abnormalities in the rostral portion of the entorhinal cortex. These abnormali-

ties extended in the anteroposterior direction to the frontobasal area rostrally, but caudally only to the level of a section through the inferior horn of the lateral ventricle and the anterior portion of the hippocampus, where the cytoarchitecture became increasingly normal. The most pronounced abnormalities were found in the anterior sections. An increased number of glia was not observed anywhere.[23-25]

Standard neuropathological methods were used.[24,26] The inferior portion of the left hemisphere, sectioned at the level of the amygdala nucleus, was embedded in celloidin; 20-µm thick celloidin sections were stained with Nissl and Heidenhain-Woelcke stains for histological investigation, and 16 cases with other clinical diagnoses were selected for use as controls. Graded series of cases and controls were used to obtain an overall view of the extent of the histological abnormalities.

The most pronounced findings were cytoarchitectural abnormalities in layers Pre-α and Pre-β; abnormalities of Pre-α in the central region often consisted of only a few characteristic island-like formations. These layers were irregularly constructed. Because the structural abnormalities were variable, a uniform pathological picture could not be obtained. While only the Pre-α and Pre-β (layer II and layer III) layers were affected in "mild" cases, the entire cortex was affected in "severe" cases. In the severe cases, layers III and IV (the Pri-layers) were depleted of approximately 20% and 40% of their neurons, respectively, in comparison with controls *(Figure 2)*.[24]

The most commonly encountered abnormalities of layer II (Pre-α) and layer III (Pre-β) appeared to be less of a quantitative than of a structural nature.[25] Two basic types of abnormality were described (heterotopic malformations):

- Absence of layer Pre-α, with only a few atypical neurons.
- Here the insular formations of Pre-α were also absent.

Together with the upper portion of layer Pre-β, layer Pre-α had often the appearance of a "double row." This consisted of a narrow upper layer, composed of a row of small neurons lying adjacent to one another, and a lower row of tightly spaced collections of groups of atypical neurons that normally do not appear at this site, clearly distinct from the pyramidal cells of layer Pre-β. These can be regarded as *heterotopic malformations*. The entire layer thus takes on a markedly "spotted" appearance. Later in our work, we therefore defined the following points as clearly pathological:

- Clusters of narrowly lying or even inseparable nerve cells. Their boundaries are often not identified.
- Often a striking difference of volume of these cells with the clusters.
- Loss of normal anatomic layering with severe thinning or complete loss of single layers, particularly layers IV and V.
- Striking intrahemispherical differences in the cytoarchitectural patterns.

Not all these points have been discussed by authors presenting "negative results."

Two distinct, well-defined types of neuronal formation found among the malformed hetereotopies of layer Pre-β will be discussed here. One of these consists of atypical pyramidal neurons, of considerably reduced volume, usually lying so close together that no separation between them was visible under the light microscope (clusters). The other type of abnormal neuronal formation consists of groups of loosely scattered fusiform bipolar neurons in layer Pre-β, which were markedly smaller and were often arranged in columns.

The histologically evident reduction of neuronal volume in layer III in schizophrenic patients can be documented with the aid of a computed analytical method. The two types of neuronal groups were encountered in alternat-

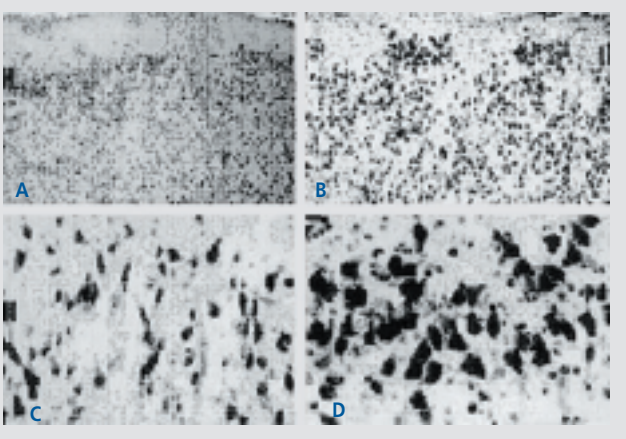

Figure 2. Focal malformation in the rostral entorhinal region in a patient with chronic schizophrenia. **A.** Rostral cortical fields in a serial histological study, fourth stage of the series, layers II and III (Pre-α and Pre-β); layer Pre-α shows irregularly scattered neurons without characteristic formation of cell islands (20 × 5). **C.** Heterotopic groups of presumably immature neurons and "clusters" in layer II Pre-β (40 × 5). **B,D.** Control sections at the same level. b. Layers Pre-α and Pre-β with typical neurons and islands (20 × 5). d. Same control structure (40 × 5); Nissl staining; celloidin embedding.

ing fashion in sections at different levels. The authors assumed that these atypical neurons, which are reminiscent of "young neurons"[17,27] in their shape and arrangement, had become stuck, as it were, in the last phase of migration and stayed in place as "ectopic" and "malformed" neurons, unable to reach their preassigned destinations in layer Pre-α. It thus appears that there may be a local disturbance of neuronal development and/or migration restricted to the rostral portion of the entorhinal area in a late phase of brain development.[24,25]

In four cases of manic-depressive illness, there were cytoarchitectural abnormalities here and in the rostral ventral portion of the insular cortex that were similar to those described in the schizophrenic psychoses, agreeing in all histological details. The common features of these two types of psychoses have been pointed out many times.[28]

The existence of structural architectural abnormalities in the rostral entorhinal cortex of patients with either type of major psychosis was confirmed by two further groups of investigators, who studied cases taken from the Yakovlev Collection.[29] Quantitative studies yielded striking findings: in eight cases of schizophrenia, five cases of cyclothymia, and eight control subjects; the number of neurons in layer II Pre-α varied from zero in severely affected cases to normal. In such cases, the cytoarchitecture of the other layers was also markedly abnormal. Neurons of layer Pre-α were displaced into layer Pre-β. No significant differences were found between the two types of major psychosis.[30]

Krimer[31] studied the entorhinal area of schizophrenic patients and controls using inadequate methods. The fixation time was excessively long (up to 1 year), and the postmortem interval (average 36 h) was unsuitable for sophisticated cytoarchitectural studies. Nonetheless, even in these authors' unclear illustrations, cytoarchitectural differences between control subjects and schizophrenics are evident.

Senitz and Beckmann were recently able to confirm the findings of Jakob and Beckmann[24,25] in a series of 20 schizophrenic cases and 22 controls. Cortical malformations of this type may have either of two possible causes:

- The neurons are unable to begin migrating.

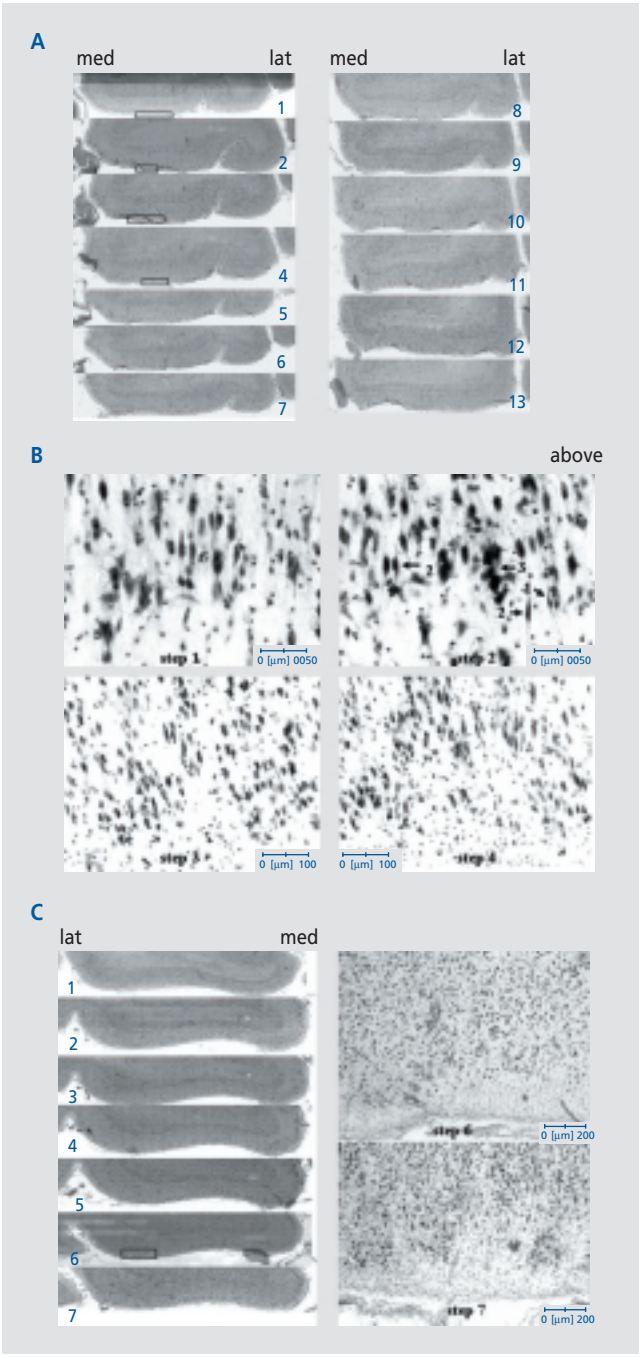

Figure 3. Affect-laden paraphrenia: *The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines (ICD-10)* F 20.3 or *Diagnostic and Statistical Manual of Mental Disorders. 4th ed (DSM-IV)* 259.3. Serial sections through rostral entorhinal cortex. **A.** Right serial sections of the celloidin embedded material. Boxes demonstrate the localization of pathological findings. **B.** High magnifications of histopathology in marked boxes in a. Step 1 depicts malformed neurons in layer II in EC. Step 2 shows "young neurons" (1); atypical neuron (2); "neuronal clusters" (3). Steps 3 and 4 show lack of the insular structure of layer II of entorhinal cortex. **C.** Left series with only minimal pathology (step 6). Normal structure of the entorhinal cortex (step 7).

• The migrating neurons remain in an ectopic position on the way to the cortex.[17,18]

The atypical neurons that do not belong to layer Pre-β seem to have encountered the second type of difficulty. Many of them are of obviously reduced volume when compared with other neurons in the same layer and with those of control subjects. These small neurons, which are often marked by a bipolar shape *(Figure 2)* or lie in layer Pre-β more as heterotopic clusters or as columns containing densely arrayed, undifferentiated neurons, seem to have become stuck along their way to the upper layer, Pre-α.[25,32] A specific histological demonstration of these neurons is not possible at present; they can be characterized only with the aid of an optimal staining technique.

These findings seem to imply that the malformation arises at a relatively late time in development. It is possible that there is a defect in the ontogenetic columns (second category).[18] The lower Pri-layers are heavily depopulated of cells in only a few cases.

In view of the spectrum of alterations seen, and the time at which migration begins in the corresponding region of the human brain, a fetal injury at some time between

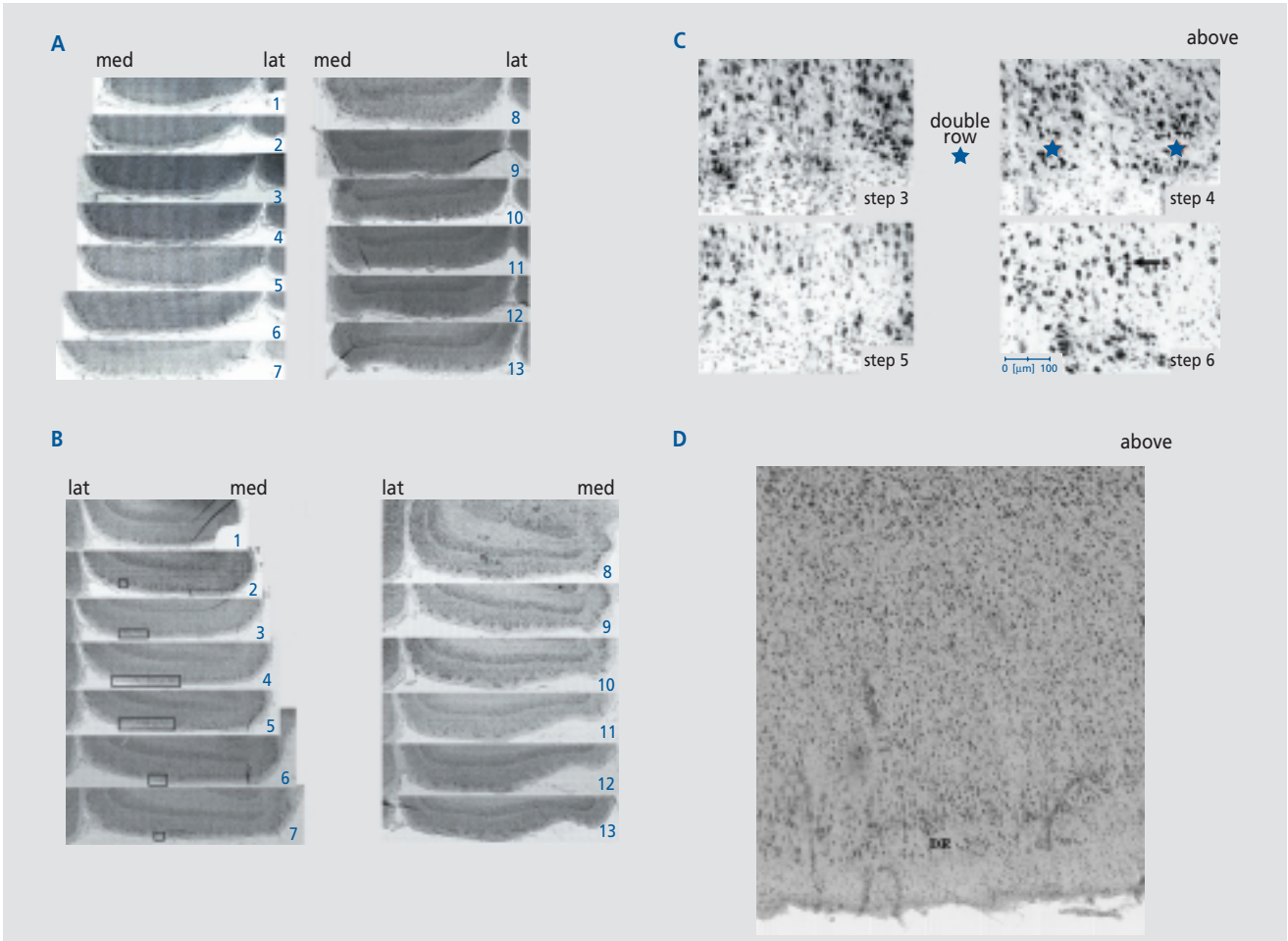

Figure 4. Negativistic catatonia: *The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines (ICD-10)* F 20.2; *Diagnostic and Statistical Manual of Mental Disorders. 4th ed (DSM-IV)* 259.2. Serial sections through rostral entorhinal cortex, celloidin embedded material. **A.** Serial sections (right) do not demonstrate pathological malformations. **B.** Boxes (left) demonstrate localizations of the pathological findings. **C.** Step 3 shows disturbed structures of layer II. Step 4 shows "double row" (stars). Step 5 shows completely disturbed layer II and atypical neurons. Step 6 shows disturbed insular region of the entorhinal cortex. Verticular columns (5) in the layer III. **D.** Histological depiction of step 7, showing complete layers of the entorhinal cortex. Disturbed structure of layer II and typical "double row" (DR).

the late third month and the fifth month of gestation can be presumed, or a genetic preprogram is at work.

Heterotopic malformations in correlation with clinical symptomatology

Since our first publication of neuropathological studies of developmental disorders in the limbic system in chronic schizophrenics,[24,25] numerous attempts have been presented to support[29,33-35] or disprove the initial findings.[26,31,36,37] In this report, we present two cases *(Table I, Figures 3 and 4)* with very different psychopathology and demonstrate the serial cuts through both hemispheres of the rostral entorhinal regions and the malformations found. We report on the different magnitude of the heterotopic malformations (for definition see page 103) either on one or both sides of the brain in correlation with clinical symptomatology.
The methods have been reported elsewhere.[24] We made serial cuts of the whole rostral entorhinal cortex on both sides.

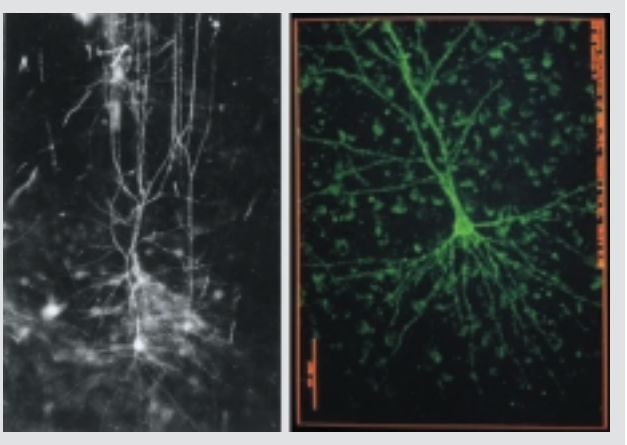

Figure 5. Orbitofrontal cortex (Brodmann area 11) in a schizophrenic patient. **A.** Low-magnification view: histological demonstration of a group of layer V pyramidal cells with multiple forked major dendrites. **B.** Detail: pyramidal cell with a single forked major dendrite. Confocal microscopy, bar 100 µm. Postmortem fluorescence technique with DiI (1,1´-dioctadecyl-3,3,3´,3´-tetramethylindocarbocyanine perchlorate).

Orbitofrontal cortex

Senitz and colleagues[38-40] used the Golgi technique as a routine method for the study of Brodmann areas 19 and 11 and were the first to find neuropathological abnormalities in the orbitofrontal region of schizophrenic patients. Because their method demonstrated the overall structure of the neurons, they were able to describe particularly striking and unusual neuronal forms:

- So-called "triangle cells" in layer VI were found to be more numerous and irregularly organized than in control cases.
- Many pyramidal cells were demonstrated in layer V that had forked major dendrites that could be followed all the way to layer II *(Figure 4)*. Dendritic duplication of this type can occur only during cortical development.
- Pyramidal cells were found in layer III that had relatively thick dendrites and were atypically long and unusually shaped, and had thick spines. The number of spines was quantitatively measured and found to be significantly elevated on a large proportion of pyramidal cells. They often lay in tufts on the surface of the major dendrite or had several forked spine heads.

The findings in these neurons presumably reflect ordinary, nonpathological histologic features that are to be regarded as plastic alterations in the area of the dendritic trunk.[41] They may be interpreted as an expression of altered functioning. Because this area is tightly linked to the rostral cortex,[6] it is possible that the abnormalities noted are due to a developmental disturbance occurring in the migratory phase as a result of the malformation in the entorhinal area. It is clear that the orbitofrontal cortex is subject both to independent, mild disturbances of development consecutively to the entorhinal disturbance and to secondary compensation effects leading to plastic alterations in the pyramidal neurons of layer III. The topography of the areas projecting to the entorhinal area is depicted in *Figure 5*. Orbitofrontal cortex and the rostral portion of the claustrocortex (insula) project onto rostral portions of the entorhinal cortex.

Patient	Gender	Age at death (y)	*ICD-10*	*DSM-IV*	Leonhard's diagnosis
Case 1 (7/26/S-44/97)	Male	76	F 20.3	259.3	Affect-laden paraphrenia
Case 2 (44/26/S-25/94)	Male	56	F 20.2	295.2	Negativistic catatonia

Table I. Gender, age at death, and the leading classifications of "schizophrenia" in two psychopathologically very different cases (case 1 *[see Figure 3]* and case 2 *[see Figure 4]*). *ICD-10, The ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders. 4th ed.*

Conclusion

In this report we made serial cuts in two cases (*Table I, Figures 3 and 4*) with very different psychopathologies, through both hemispheres of the rostral entorhinal regions. We report on the different magnitude of the heterotopic malformations found, either on one or both sides, in correlation with the clinical symptomatology. The methods used have been reported elsewhere.[24]

We conclude that this is possibly the main reason why we see such differences in the clinical picture and course of the so-called endogenous psychoses.
Further data are needed to make a one-to-one comparison between prominent psychopathologies and the site of the heterotopic malformations in the rostral entorhinal region. ❑

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El concepto emergente de "psicosis endógenas"

En los últimos decenios se han descrito varias alteraciones estructurales en los cerebros de los pacientes con "psicosis endógenas". La mayoría de los pacientes esquizofrénicos muestra una dilatación de los ventrículos laterales y defectos estructurales sutiles en las estructuras temporobasal y orbitofrontal (hipofrontalidad). Hemos examinado la citoarquitectura de estas importantes estructuras centrales, a saber la región entorrinal y la corteza orbitofrontal (área 11 de Brodmann), objeto de una meticulosa investigación en nuestros laboratorios durante los últimos decenios. Efectuamos cortes seriados a ambos lados de toda la porción rostral de la corteza entorrinal. Para este informe seleccionamos dos casos con aspectos psicopatológicos muy distintos y presentamos los cortes seriados a través de sendos hemisferios así como las malformaciones halladas. Se comenta la magnitud diferente de las malformaciones heterotópicas, bien a ambos lados o sólo en uno de ellos.

Le développement du concept de « psychoses endogènes »

Plusieurs déviances structurales ont été décrites ces dernières décennies dans les cerveaux des patients atteints de " psychose endogène ". La majorité des patients schizophrènes présente de façon bien établie une dilatation des ventricules latéraux et des déficits structuraux subtils dans les structures frontales orbitales et temporobasales (hypofrontalité). Nous avons examiné l'architecture cytologique de ces importantes structures centrales, à savoir la région entorhinale et le cortex orbitofrontal (aire 11 de Brodmann) qui ont fait l'objet de recherches méticuleuses dans nos laboratoires ces 10 dernières années. Dans une nouvelle série de patients schizophrènes et de témoins normaux, nous avons pratiqué des coupes en série bilatérales du cortex rostral entorhinal entier. Pour cet article, nous avons sélectionné deux cas avec des psychopathologies très différentes et nous présentons les coupes effectuées sur les deux hémisphères et les malformations trouvées ainsi que les différentes tailles des malformations hétérotopiques uni- ou bilatérales.

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