Five discoveries of Volodymyr Betz. Part one. Betz and the islands of entorhinal cortex

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Abstract: *in the series of publications, which this article opens, we consider five fundamental neuromorphological observations of our compatriot, the classic of world neuroscience, Volodymr Betz. For four of them, we demonstrate the status of discoveries for the first time, for the other one — the giant pyramidal neurons of the motor cortex — despite its widespread and long-standing recognition, we reveal the limitations of modern knowledge and ideas. Two of the mentioned observations — giant fusiform, or spindle-shaped neurons of the cingulate and insular cortex and islands of the entorhinal cortex — are currently known only to a narrow circle of specialists; to the others two, cytoarchitectonic description of the olfactory tubercle and some sings of the modular cortex organization, we pay attention for the first time. In this, the initial part of the series, exposing modern apprehensions about the structure and functions of the entorhinal cortex, we demonstrate the weight of Betz's pioneering observation of extraordinary neu- ron clusters, which are nowadays known as entorhinal islands, and prove the fact of recognizing his historical priority in the description of these amazing brain structures.*

Key words: history of medicine, neurosciences, entorhinal cortex, grid cells, memory, episodic, time perception, alzheimer disease.

Introduction

Higher mental functions, including memory, consciousness and the inner world, the sense of time and error-free spatial navigation, are among the most attractive, if not obsessive, topics of human cognition. The last century revealed some details of the arrangement of the material apparatus, which assists the realization of these psyche functions. In the core of this machinery is a small part of the brain - the entorhinal cortex. The study of its structure and function is now quite inten-sive, probably not least due to the fact that it is also present in lower mammals and is therefore available for all modern tools of experimental neurophysiology. So, at the moment, it is difficult to imagine a neuroscientist who has not seen at least one work devoted to the entorhinal cortex during his professional career. This area of the brain became famous in 2014, because it was for the study of the neurons of the entorhinal cortex that the Nobel Prize was awarded that year. And also the entorhinal cortex is the debut scene of

Alzheimer's disease.

It so happened that our compatriot, who, as is known, was well-informed and sympathetic to the history of his own people, made a large-scale addition to the study of entorhinal piece of cortex. Historiographic investigations have always been an important segment of the scientific process, since, in addition to issues of honor and respect (without which the development of science, unfortunately, is unthinkable), they reveal the very drama of knowledge in all its unsightly.

It is probably symbolic and appropriate that this material comes out precisely at this difficult time for Ukraine; a time not only and not so much of survival, but also, for the majority - of the second birth or even the metamorphosis of the Ukrainian people. It is at such moments that the examples of success are superimportant. And here is an example of world-class success is Volodymyr Betz.

In this work, we sought to fully reveal the depth and providential significance of his observations regarding the microstructure of the entorhinal cortex, observations, that are recognized, as it turned out, in the neurobiological environment. And for the first time to demonstrate his own preparations of this brain area, which became the basis of his published morphological descriptions and generalizations.

Aim

To demonstrate the Betz priority of in the discovery of entorhinal islands, to determine the importance and relevance of this discovery.

Materials and methods

To determine the relevance and degree of study of entorhinal islands, we used the method of searching and summarizing scientific information. Scientific articles in specialized periodicals, available in the PubMed database, in network electronic catalogs and in the funds of the National Scientific Medical Library of Ukraine, as well as thematic scientific publications in book format, available on the Internet or on market Internet services among the assortment of printed publications, were selected as the subject of the search. When selecting the material, the principles of actuality, reliability, objectivity, informational unity and relevance were taken into account. We used the historical method (*including the chronological approach*) to find out the carrier of priority in the discovery of the entorhinal islands.

From the point of view of the methodology of the scientific process, when working on the material of the article, we used routine methods — analysis, synthesis, abstraction, analogy, comparison, as well as a systematic approach.

Also, using the method of subject morphological search based on given cytoarchitectonic criteria among the collection of Betz neurohistological preparations, which is kept at the Department of Descriptive and Clinical Anatomy of the Bogomolets National Medical University, we found the temporal lobe pole preparations, where entorhinal islands were identified. Photofixation and scaling of histological images of the relevant areas was performed in the Neuropathomorphology Department electron microscopy laboratory of the State Institution «Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine» on an Axiophot optical microscope (Opton, Germany), using a Canon 600 digital camera (Canon Inc., Taiwan), computer analyzer CAI-01ABH (Selmi, Ukraine), software «Kappa opto-electronics GmbH» (Germany) and a object-micrometer. Delicate optimization of images in order to achieve equivalence of their color characteristics carried out with MS Power Point tools on a personal computer.

1.1. Brain Navigation System

The Nobel Prize of 2014 confirmed significance of the mammals' navigation system characteristics. At this time, a significant number of brain cells have been described, the activity of which correlates with the realization of this function certain aspects (*Tab. 1*). Perhaps it currently includes neurons whose unique status in providing certain nuance of navigation will be disproved over time. However, it is important that huge proportion of these cells was detected exactly in the entorhinal cortex. So, let's dwell on the peculiarities of this small area of the brain arrangement.

1.2. Entorhinal Cortex

The term "*entorhinal cortex*" was suggested by Korbinian Brodmann (*R. Insausti & Amaral, 2012*), probably, because this region (*Brodman's areas 28 and 34*) in a human is located more medially, more interiorly from the rhinal sulcus and perirhinal cortex (*fig. 1*). In primates it is local-

Table 1. Currently Known Neurons of the Mammals' Brain Navigation System

Type of the cells	Localization in the brain	The organism for which the presence of these cells has been established	Main references
grid cells	medial entorhinal cortex (MEC), particularly its II layer, and the parasubiculum	rodents, probably human	*Hafting, Fyhn, Molden, M.B. Moser and E.I. Moser, 2005; Fyhn, Hafting, Treves, M.B. Moser and E.I. Moser, 2007; Yartsev, Witter and Ulanovsky, 2011; Killian, Jutras and Buffalo, 2012; reviewed by: E.I. Moser, M.B. Moser and McNaughton, 2017, and Tukker et al., 2022*
place cell	CA1 *(Cornu Ammonis, field 1)* and CA3 field of the hippocampus	rodents	*O'Keefe and Dostrovsky, 1971; reviewed by: E.I. Moser et al., 2017*
head direction cells *(including pure azimuth cells and pure pitch cells in a bat)*	MEC, presubiculum, post-subiculum, anterodorsal thalamic nucleus, lateral mammillary nucleus, dorsal tegmental nucleus	rodents, bats, primates	*Taube, Muller and Ranck Jr, 1990 a, b; Mizumori and Williams, 1993; L.L. Chen, Lin, Green, Barnes and McNaughton, 1994; Taube, 1995; Stackman and Taube, 1998; Sargolini et al., 2006; Giocomo et al., 2014; Finkelstein et al., 2015; Shinder and Taube, 2019; Angelaki and Laurens, 2020; reviewed by Tukker et al., 2022*
angular head velocity cells	list of the brain locations of these cells is less numerous than that for ordinary head direction cells	rodents	*reviewed by Taube, 2009*
conjunctive cells	MEC	rats	*reviewed by Tukker et al., 2022*
boundary cells, border cells	presubiculum, parasubiculum, the II, III and V layers of the entorhinal cortex	rodents	*Savelli, Yoganarasimha and Knierim, 2008; Solstad, Boccara, Kropff, M.B. Moser and E.I. Moser, 2008; Tang et al., 2014; Tang et al., 2015; reviewed by Tukker et al., 2022*
path cells	entorhinal cortex	human	*Jacobs, Kahana, Ekstrom, Mollison and Fried, 2010*
cue cells	MEC	mice	*Kinkhabwala, Gu, Aronov and Tank, 2020*
object-vector cells	MEC	mice	*Høydal, Skytøen, Andersson, M.B. Moser and E.I. Moser, 2019; reviewed by Tukker et al., 2022*

speed cells, as well as the angular and linear speed cells	*speed cells* — MEC, field CA1 and CA3 of the hippocampus; at least some of them belong to the place cells and the grid cells; *angular and linear speed cells* — MEC, presubiculum, parasubiculum	rodents	*C. Sun et al., 2015; Kropff, Carmichael, M.B. Moser and E.I. Moser, 2015, and Spalla, Treves and Boccara, 2022; reviewed by Tukker et al., 2022*
time cells	CA1 and CA3 fields of the hippocampus, probably, MEC *(Salz et al., 2016)* and lateral entorhinal cortex (LEC; *Tsao et al., 2018; Rolls and Mills, 2019)*	rodents	*Salz et al., 2016; Tsao et al., 2018; reviewed by Rolls and Mills, 2019*
spatial view cells	in primates — fields CA1 and CA3 of the hippocampus, parahippocampal gyrus, presubiculum	primates, human, probably rodents	*Robertson, Rolls and Georges-François, 1998; reviewed by Rolls, 2021*
egocentric bearing cells	medial temporal cortex, particularly parahippocampal cortex	human and other mammals	*Kunz et al., 2021*
allocentric bearing to a landmark neurons	in a macaque -— parietal cortex *(Brodman's area 7a)* and posterior cingulate cortex	primates, probably human, rodents	*reviewed by Rolls, 2021*
movement cells	posterior parietal cortex	rodents	*Rochefort, Lefort and Rondi-Reig, 2013, based on Whitlock et al., 2012*
whole body motion cells	hippocampus, subiculum	primates, possibly human, rodents	*reviewed by Rolls, 2021*
goal-direction cells, goal-distance cells	CA1 field of hippocampus	bat	*Sarel, Finkelstein, Las and Ulanovsky, 2017*
3D border cells, 3D head-direction cells, 3D grid cells	presubiculum *(3D head-direction cells)*, MEC *(3D border cells, 3D head-direction cells, 3D grid cells)*	bat	*Finkelstein et al., 2015; Ginosar et al., 2021*
navigation cells of subiculum: axis-tuned cells, barrier-related cells, boundary vector cells, multiplexed place cells	subiculum	rat	*reviewed by N. Matsumoto, Kitanishi and Mizuseki, 2019*
social place cell	field CA1 of hippocampus	rat, bat	*Danjo, Toyoizumi and Fujisawa, 2018; Omer, Maimon, Las and Ulanovsky, 2018*

ized on the ventromedial surface of the temporal lobe anterior part, bordering with periamygdaloid cortex, presubiculum and parasubiculum, perirhinal cortex and the rest of the parahippocampal gyrus cortex (*Kobro-Flatmoen & Witter, 2019*). It contains 6 layers, but refers to the transitional cortex — periarchicortex (*Stephan, 1975*). The total number of neurons of the entorhinal area in a human hemisphere makes up 7–8•10^6 (*R. Insausti & Amaral, 2012; Naumann et al., 2016*).

Two main parts of the entorhinal cortex are distinguished: in rodents — medial (*medial entorhinal cortex, MEC*) and lateral (*lateral entorhinal cortex, LEC*), in a human — posteromedial (*pMEC*) and anterolateral (*aLEC*) (*R. Insausti & Amaral, 2012; Kobro-Flatmoen & Witter, 2019*). Traditionally, the MEC and pMEC, LEC and aLEC are considered homologous (*Navarro Schroder, Haak, Zaragoza Jimenez, Beckmann & Doeller, 2015; Ohara et al., 2021, and many other works*).

The II layer of the entorhinal cortex is the most interesting from many points of view. Within the MEC borders it contains two types of neurons — stellate and pyramidal (*reviewed by Witter, Doan, Jacobsen, Nilssen & Ohara, 2017; Tukker et al., 2022*). The ***pyramidal ones*** are predominantly excitatory, expressing calbindin or wolframin (*wolfram syndome protein 1*); they represent 30–40 % of all MEC type II neurons, preferentially projected on the CA1-neurons, demonstrate a clear dependence of activity on a θ-rhythm, and receive cholinergic inputs (*reviewed by Naumann, Preston-Ferrer, Brecht, & Burgalossi, 2018*). The ***stellate neurons*** are the excitatory ones, express Reelin, represent up to 50–60 % of all MEC layer II neurons, and being a basic source of the perforant fibers which make synapses with the granule cells of the dentate gyrus (*reviewed by Naumann et al., 2018*). The LEC layer II also contains two basic neuron phenotypes (*Witter, Doan, et al., 2017*) — *Reelin*-positive (*analogues of the MEC layer II stellate neurons*) and calbindin-positive ones (*analogues of the MEC layer II pyramidal neurons*).

The entorhinal cortex afferents come from the perirhinal, piriform, cingulate, insular and orbitofrontal cortex, from other regions of parahippocampal cortex and from the superior temporal gyrus cortex (*Van Hoesen, Pandya & Butters, 1972;*

R. Insausti, Amaral & Cowan, 1987; R. Insausti & Amaral, 2008, 2012; Witter & Amaral, 2021), as well as the medial part of the septal complex (*Jacob, Poucet, Liberge, Save & Sargolini, 2014*) and, probably, from the amygdaloid complex, basal forebrain, thalamus, **supramammillary nucleus**, ventral tegmental area, raphe nuclei and from the locus coeruleus (*R. Insausti & Amaral, 2012*).

The main efferents of the entorhinal cortex make a perforant path, which mainly consists of the layer II and III neuron axons (*Xu, Y. Sun, Holmes & López, 2016; Witter, Kleven & Kobro Flatmoen, 2017*). At that, the *Reelin*-positive stellate glutamatergic neurons of layer II project into the dentate gyrus, hippocampal field CA3 and CA2 (*Naumann et al., 2018; Matsumoto et al., 2019; Nilssen, Doan, Nigro, Ohara & Witter, 2019*), while the calbindin-positive pyramidal glutamatergic neurons of layer II project into the field CA1 and subiculum (*R. Insausti & Amaral, 2012; Nilssen et al., 2019*), producing the so-called temporo-ammonic pathway (*Witter, Kleven et al., 2017*). It was for the glutamatergic synapses of the perforant path axons with the dentate gyrus granule cell dendrites of the rabbit, that the long-term potentiation was described (*Lømo, 1966; Bliss & Lømo*, 1973) — which is one of the most probable electro-physiological correlates of memory and learning (*Abraham, Jones & Glanzman, 2019; Bliss & Collingridge, 2019; Joshi, Patel, Rehan & Kuppa, 2019; Dringenberg, 2020*).

It is obvious that the connections of the entorhinal cortex are wider than those listed (*Ohara et al., 2019, 2021; Guthman et al., 2020; Hu, C.H. Chen, S.Q. Chen & Ding, 2020; Meier, Q. Wang, Ji Ganachaud & Burkhalter, 2021; Huang, Rolls, Hsu, Feng & Lin, 2021; Raithel & Gottfried, 2021; Syversen et al., 2021*) and cover distal cortex areas, e.g., primary somatosensory cortex (*C. Wang et al., 2020*) and *area prostriata* (*Hu et al., 2020*).
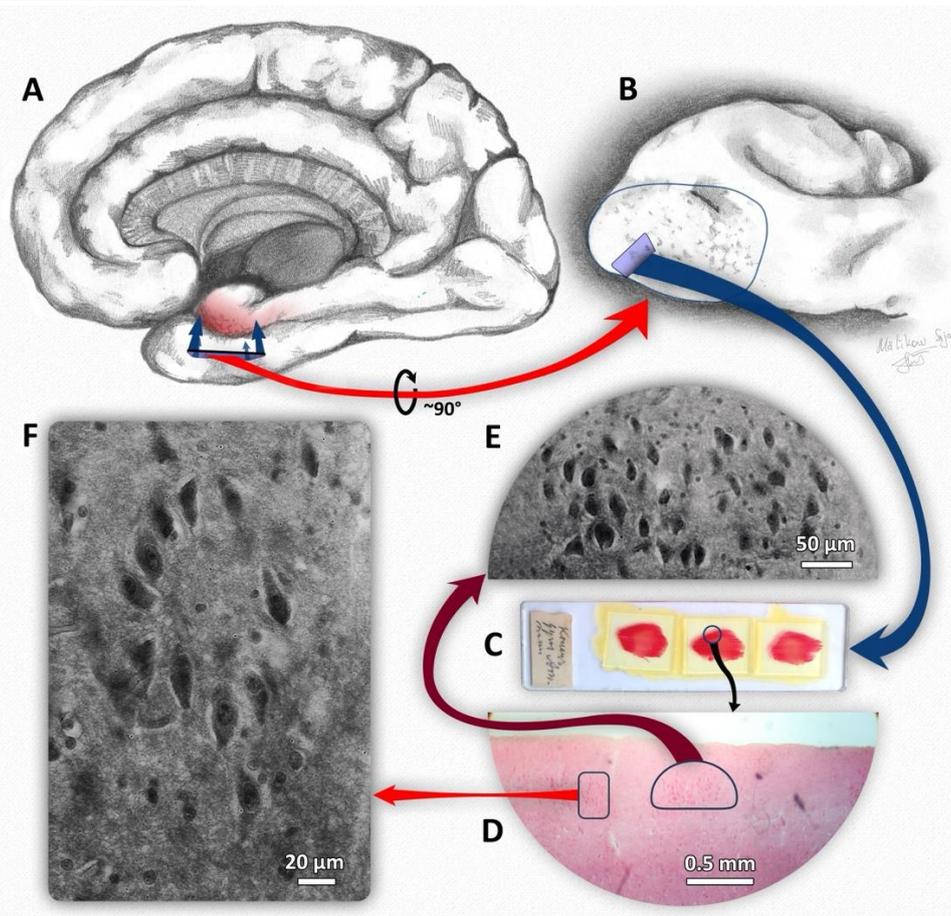
Fig. 1. Human entorhinal cortex and its main morphological peculiarities. *Scheme-collage*.

A — Schematic image of the human entorhinal cortex localization in the right brain hemisphere. The approximate location of Brodmann areas 28 and 34, corresponding to the entorhinal cortex, is highlighted with a pink-red planar gradient fill.

B — View on the uncus region of the temporal lobe from below and from the median plane of the brain with visualization of the entorhinal tuberosity, resembling a coarse-meshed rough surface (*outlined with a dirty blue loop*). For our original reproduction of the macroscopic view of the human entorhinal cortex, shown in fig. 1A and 1B, images of this brain region in the works of Duvenroy, 1988 (*fig. 17, 20 and 52*), Simic et al. (*2005, fig. 1 C*), and in the *https://en.wikipedia.org/wiki/Brodmann_area_34*, and *https://en.wikipedia.org/wiki/Brodmann_area_28*, were used as samples.

C — Betz's preparations, obtained, according to his own signature, from the «*end of Ammon's gyrus*» (*fig. 3 A, extreme histological slide on the right*). On each carmine-stained section, the cortex (*deep red*) and white matter of the brain (*lighter*) are clearly visible. The location of the cortical sections presented on the Betz preparation is shown by us in fig. 1 B arbitrarily.

D — Entorhinal cortex (*in our deep convinsion*) on one of Betz's preparations under low magnification (*a complete image of this field of view is shown in fig. 3 B*). In the near-surface layer of the cortex at a shallow depth, three neuronal clusters are well visualized, two of which are shown in an enlarged view in fig. 1 E and fig. 1 F. The section of the cortex shown here (*fig. 1 D*) in an enlarged form on the Betz preparation is labeled arbitrarily.

E — The entorhinal island (*in our deep convinsion*), outlined in fig. 1 D by a semicircular loop, in an enlarged view, after black-and-white stylization using Adobe Photoshop tools to contrast large neurons. The shape and arrangement of these neurons creates the impression, in Betz's words, of "*rows of thread in a ball*", which corresponds to the term he proposed to designate this kind of clusters — "*glomerula corticalia*". In its native form, this neuronal claster is shown in fig. 4 A.

F — The entorhinal island (*in our deep convinsion*), outlined in fig. 1 D by a rectangular loop, in an enlarged view, after black-and-white stylization using Adobe Photoshop tools to contrast large neurons. In its native form, this neuronal cluster is shown in fig. 5 A (*when viewed from left to right and top to bottom — fourth column, third row*).

The brain drawings used in fig. 1 A and fig. 1 B were made by Ziia Melikov, the collage was created by Volodymyr Medvediev and Anna Medvedieva.

1.3. Clusters of Entorhinal Cortex

The most interesting characteristic of the entorhinal cortex is its modular composition, which is manifested through clusters of the layer II neurons, or by clusterization of layer II neuronal population. Two types of clusters have been described: the MEC/pMEC contains the so-called *patches* (*cell patches*), with the small pyramidal neurons, while the LEC/aLEC contains the so-called *islands*, *nests* or *glomeruli* (*fig. 1 E, F*), filled basically with the stellate neurons. This islands in humans have a macroscopic counterpart — *tubercles* (*eminences, elevations*), also known as *bumps*, or *warts* (*verrucae*) of the entorhinal cortex surface (*fig. 1 C; see further*).

1.3.1. Islands

The islands of the LEC/aLEC layer II, or **entorhinal islands** are detected already by ordinary neurohistological staining (*Braak, 1972; fig. 1 E, F*). Analogous structures are visualized when identifying the expression of various enzymes, proteins and peptides (*Solodkin & van Hoesen, 1996; Mikkonen, Soininen & Pitkänen, 1997*). Some authors state, that the majority of the human entorhinal islands contain stellate cells, surrounded with a parvalbumine-positive neuropil (*Beall & Lewis, 1992; Hevner & Wong-Riley, 1992*). The diameter of an entorhinal island of the human aLEC is ~0.5–1 mm, and the mean distance between them is 369 ± 162 μm (*Solodkin & Van Hoesen, 1996*). An average number of neurons in one island of the left and right human hemisphere is, respectively, ~$4.7 \cdot 10^5$ and ~$4.1 \cdot 10^5$ (*Simic et al., 2005*). The entorhinal cortex of the human left hemisphere contains ~121 macroscopic islands analogues — the entorhinal tubercles, the right one — ~111, which overall makes — ~232 (*Simic et al., 2005*).

1.3.2. Patches

The MEC/pMEC layer II contains immunohistochemically detectable clusters of pyramidal neurons, which are named **entorhinal patches**. Detection of these patches using ordinary light-optic examination methods is almost impossible for rodents and dogs (*Woźnicka, Malinowska & Kosmal, 2006*), though, quite real for a human and primates (*Beall & Lewis, 1992, fig. 5 A, 6 A*). Beside pyramidal neurons, the patches contain other neurons types (*Ray et al., 2014;*

Naumann et al., 2016); in particular, the human patches contain also stellate neurons (*Naumann et al., 2016*). The total number and average diameter of an entorhinal patches in one rat brain hemisphere are, respectively, 69 ± 17 units and 145 ± 41 μm, in a one human hemisphere — 115 ± 16 units and 532 ± 197 μm. The average number of calbindin-positive neurons in an entorhinal patch of a rat is 111 ± 42 cells, that of a human — 837 ± 84 cells (*reviewed by Naumann et al., 2016*). On the tangential section, the patches make hexagonal, rectangular and geometrically irregular structures, which in a human are divided in such proportion: ~45 %, ~35 % and ~20 %, respectively, or, by other calculations, — ~50 %, ~30 % and ~20 % (*reviewed by Naumann et al., 2016*).

1.3.3. Tangential Localization of Islands and Patches

Entorhinal islands and patches do not overlap in space (*Naumann et al., 2016, fig. 8 A*). Sporadic observations in human and other higher mammals (*Ramon y Cajal, 1988, work of 1901–1902, p. 301, fig. 15; Beall & Lewis, 1992, fig. 5 A, 6 A; Suzuki & Porteros, 2002, fig. 6 B, fig. 8*) evidence about opportunity of both clusters identification within one optical field, and besides, when the human islands and patches take the same tangential position, in some places it produces an impression of various depth of their occurrence (*Naumann et al., 2016; fig. 8 A*). Such assumption is confirmed by the earlier data, received for the entorhinal cortex of the human and apes (*Beall & Lewis, 1992, fig. 5 A, 6 A; Suzuki & Porteros, 2002, fig. 6 B, fig. 8*).

1.3.4. Patches and Islands in Other Areas of the Cortex

It is well known, that the tangential clusters of neurons, similar with the entorhinal patches, are characteristic for other various cortex regions, the list of which is given in many works (*see Horton & Adams, 2005; Rockland, 2021; Tukker et al., 2022*). What is less thoroughly studied, is the cortical prevalence of clasterization, characterizing layer II of the LEC/aLEC. At present, such type of clasterization in mammals has been also described for the uncal cortex, subiculum, presubiculum and parasubiculum (*Hevner & Wong-Riley, 1992; Heinsen et al., 1994; von Economo, 2009,*

p. 150–169; R. Insausti & Amaral, 2012; Ding, 2013; R. Insausti, Muñoz-López, A.M. Insausti & Artacho-Pérula, 2017), as well as for many other areas of the cerebral cortex of those mammalian species that are not used in experimental medicine (*Hof & van der Gucht, 2009; Butti & Hof, 2010; Butti et al., 2014; Raghanti et al., 2015; Raghanti et al., 2019*) — hump-backed whale (*Megaptera novaeangliae*), fin whale (*Balaenoptera physalus*), minke whale (*Balaenoptera acutorostrata*), beluga whale (*Delphinapterus leucas*), bottlenose dolphin (*Tursiops truncatus*), Florida manatee (*Trichechus manatus latirostris*), Atlantic walrus (*Odobenus rosmarus rosmarus*), river hippopotamus (*Hippopotamus amphibius*), pigmy hippopotamus (*Hexaprotodon liberiensis*), Western bongo (*Tragelaphus eurycerus*), white-tailed deer (*Odocoileus virginianus*), domesticated pig (*Sus scrofa domesticus*), and a horse (*Equus ferus caballus*).

1.4. Entorhinal Patches and Grid Cells

The most thoroughly studied functional type of the MEC neurons are the grid cells (*Hafting et al., 2005*), for the discovery of which E.I. Moser and M.B. Moser were awarded the Nobel Prize in physiology and medicine in 2014. A peculiar trait of these neurons is their maximum firing rate when the animals is moving through the special plane points — nodes of the grid formed by the apices of imaginary regular triangles assembled into hexagonal figures. In this way, each grid cell possesses its own map of the fiducial locomotion plane points (*Hafting et al., 2005*), which is quite flexible (*Fyhn et al., 2007; Krupic, Bauza, Burton, Barry & O'Keefe, 2015; Ismakov, Barak, Jeffery, Derdikman, 2017; Krupic, Bauza, Burton, O'Keefe, 2018*), and that which may deform due to the memorized goal representation (*Boccara, Nardin, Stella, O'Neill & Csicsvari, 2019*), considering the target-related reward information (*W. Wang & W. Wang, 2021*) and being represented in various scales (*reviewed by: E.I. Moser et al., 2017*). The prevalent position of the grid cells is in the MEC layer II (*reviewed by: Tukker et al., 2022*). Nowadays, it is possible to state, though with some precautions, about the existence of similar mechanism metrification of neighbourhood in human (*Doeller, Barry, & Burgess, 2010; Bellmund, Deuker, Navarro Schröder,*

& Doeller, 2016; Horner, Bisby, Zotow, Bush, & Burgess, 2016; Constantinescu, O'Reilly, & Behrens, 2016; Nau, Navarro Schröder, Bellmund, & Doeller, 2018; Julian, Keinath, Frazzetta, & Epstein, 2018; D. Chen et al., 2018; Maidenbaum, Miller, Stein & Jacobs, 2018; Staudigl et al., 2018; He & Brown, 2019; Kim & Maguire, 2019; Bellmund et al., 2020; W. Wang & W. Wang, 2021).

The data about the morphological and immunohistochemical phenotype of the grid cells are sparse. It is admitted, that the grid cells account for 18 % of the MEC neurons, border cells — 9 %, head direction cells — 1 %, and the non-classified space-dependent cells — 68 % (*Diehl, Hon, Leutgeb & Leutgeb, 2017*). According to Miao, Cao, M.B. Moser and E.I. Moser (*2017*), among all identified grid cells in the mice, 94 % were identified in the MEC, and slight portion — in presubiculum. At that, 33 % of the grid cells were in layer II of the MEC (*~9 % of the layer neurons*), 31 % — in layer III (*~6 % of the layer neurons*), and 36 % — between the layers (*Miao et al., 2017*). Overall, the proportion of the grid cells among all MEC neurons makes up 10–20 % (*Naumann et al., 2018*), that one among the pyramidal neurons — 19% (*Tang et al., 2014*), and among the stellate neurons — about 3–25 % (*Tang et al., 2014; Rowland et al., 2018*).

Currently, the mechanism of formation of the typical spatial-preferential grid cell activity is unidentified (*Witter, Doan, et al., 2017; Naumann et al., 2018; Tukker et al., 2022*), the evidence about contribution of the stellate and pyramidal neurons of the MEC layer II in the formation of the grid cell specific activity is fragmental (*Naumann et al., 2018*), and the mechanisms of interdependence of the various navigation system cell are shrouded in darkness (*E.I. Moser et al., 2017; Rowland et al., 2018; Angelaki & Laurens, 2020; Tukker et al., 2022*), and the role of visual and other types of information for the peculiar grid cell activity is the subject of hypotheses (*Connor & Knierim, 2017; Campbell & Giocomo, 2018; Jacob, Capitano, Poucet, Save, & Sargolini, 2019; Jayakumar et al., 2019; Moon, Gauthier, Park, Faivre & Blanke, 2022; Waaga et al., 2022*). Although, there exists a considerable number of models, aimed to answer this questions (*Finkel-*

stein et al., 2015; Igarashi, 2016; E.I. Moser et al., 2017; Naumann et al., 2018; Widloski, Marder & Fiete, 2018; Kang & Balasubramanian, 2019; Mosheiff & Burak, 2019; Park, Jang, Kim & Kwag, 2019; Rodríguez-Domínguez & Caplan, 2019; Spalla, Dubreuil, Rosay, Monasson, & Treves, 2019; Agmon & Burak, 2020; D'Albis & Kempter, 2020; Ekstrom, Harootonian & Huffman, 2020; Vinepinsky, Perchik, & Segev, 2020; Waniek, 2020; Krishna et al., 2021; Rueckemann, Sosa, Giocomo & Buffalo, 2021; T. Wang, Yang, Z. Wang, Zhang & W. Wang, 2021; Tukker et al., 2022 and many others). This situation is caused by impossibility of comparing various phenotype brain cells characteristics: functional, morphological and immunohistochemical ones (*Hardcastle, Ganguli & Giocomo, 2017; Naumann et al., 2018*). Modern studies gradually help us cope with this methodological difficulty; so, the most probable is the toroidal functional network topology of the MEC cells population (*Gardner et al., 2022*).

Another key issue of the brain navigation system physiology is the correlation of the tangential, often hexagonal distribution of the entorhinal cortex layer II modular structures with the ability to hexagonally mapping of the planar neighbourhood by the located here grid cells (*Naumann et al., 2018*). The search for an answer to this question has not yet been successful yet (*Igarashi, 2016; Gu et al., 2018; Naumann et al., 2018*). It is important to note, that the tangentially clustered in patches pyramidal neurons of the MEC layer II may play a significant role in the grid cell activity formation (*Naumann et al., 2016*). Simultaneously, tangential clustering of the MEC grid cells, if present, is different (*Naumann et al., 2018; Gu et al., 2018; Obenhaus et al., 2022*).

1.5. Functions of the LEC/aLEC

The entorhinal islands function remains unidentified.

The paraentorhinal projections of calbindin-positive neurons of the LEC layer II, and, probably, LEC itself, are wider than those of the analogous cells of the MEC layer II and MEC itself (*Ohara et al., 2019*). The LEC receives significant convergent inputs from the perirhinal cortex and postrhinal cortex to all main neurons of the II layer, which allows this part of the brain

to take into account continuous changes in the behavioral environment (*Doan, Lagartos-Donate, Nilssen, Ohara & Witter, 2019*), e.g., changes in the elemental composition of the environment (*Tsao, M.B. Moser & E.I. Moser, 2013*). Regarding this, it is important that the LEC is directly associated with the olfactory bulb and piriform cortex (*Igarashi et al., 2012; Liu, 2020*), the neuronal networks of the LEC layer II are involved in the processing of olfactory information (*Bitzenhofer, Westeinde, Zhang & Isaacson, 2022*), and the LEC altogether participates in odor-context associations (*Persson et al., 2022*). Probably, due to this, certain LEC neurons are preferentially activated in the case of animal close location to a new, limited in space, object (*Deshmukh & Knierim, 2011; Tsao, M.B. Moser & E.I. Moser, 2013*). Oscillations with a frequency of 20–40 Hz, which are the electrophysiological equivalent of the functional connection of the LEC and hippocampal field CA1 during the engramming of certain specific information (*Igarashi, Lu, Colgin, Moser & Moser, 2014; Igarashi, 2015*), can be generated precisely with the participation of the olfactory bulb and piriform cortex (*reviewed Igarashi, 2016*). Finally, modulation or mediation by the LEC of cortical γ-oscillations associated with the θ-rhythm is an important condition for memorizing or reproducing spatially-connoted information (*Luo et al., 2022*).

Nilssen et al. (*2018*), and Nilssen et al. (*2019*) suggest that the LEC may contain similar to the MEC neuronal network and cells with similar to the grid cells spatial-preference activity, which provide metrification of the LEC-specific object-dependent information about environment. Witter, Doan et al. (2017) consider that the LEC provides connection of the hippocampus with the anterior parts of the cortex, mediating access to the information about movement contextual changes, including information about transformation of the environment.

The LEC/aLEC is a key node of the episodic (*Bellmund, Polti, & Doeller, 2020, Vandrey et al., 2020; Takehara-Nishiuchi, 2022*) and social (*Dang et al., 2022; Lopez-Rojas, de Solis, Leroy, Kandel, & Siegelbaum, 2022*) memory, provides fast information reproduction under similar context (*Pilkiw, Jarovi & Takehara-Nishiuchi, 2022*),

participates in detecting familiarity for events (*Mahnke, Atucha, Pina-Fernàndez, Kitsukawa & Sauvage, 2021*), in time association of the stimuli which are applied in a certain sequence (*Yu, Yu, Choi & Takehara-Nishiuchi, 2021*), in engramming and reproduction of the temporal information, summarized in the LEC according to the acquired behavioral experience (*Tsao et al., 2018; Bellmund, Deuker & Doeller, 2019; Bellmund, Polti, & Doeller, 2020*), and finaly, in producing the space-time map of the experienced events (*Deuker, Bellmund, Navarro Schröder & Doeller, 2016; Bellmund et al., 2019; Montchal, Reagh & Yassa, 2019; Bellmund, Polti, & Doeller, 2020*). The LEC may also play a role in the mechanisms of fear memory (*East Jr., Brady & Quinn, 2021*) and neuropathic pain syndrome (*Guida et al., 2022*), in the formation of spatial correlates of feeding behavior (*Azevedo et al., 2019*) and participate in the motivation sphere function and in the network reinforcement correlates formation (*Issa, Radvansky, Xuan, & Dombeck, 2024*).

With all this, it turns out that synapses of LEC axons with newly formed dentate gyrus granule cells acquire the ability to form long-term potentiation not immediately, but after several months (*Vyleta & Snyder, 2021*) and, most interestingly, LEC has a significant, but still poorly studied effect on the motor system (*Ionov, Pushinskaya, Gorev & Frenkel, 2020*).

1.6. Functions of the Entorhinal Cortex in General
1.6.1. Space

The representation of "spatiality" in the sphere of consciousness is provided with the participation of a number of brain areas — the orbitofrontal cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, cortex of the inferior parietal lobule, posterior cingulate cortex, medial temporal cortex, entorhinal cortex, hippocampus, anterior thalamus, claustrum, and cerebellum (*Rochefort et al., 2013; Bareš et al., 2019; Cona & Scarpazza, 2018; Schafer & Schiller, 2018; O'Mara & Aggleton, 2019*).

To date, a number of indirect evidences have been obtained for the participation of the hexagonal metrification system (*Doeller et al., 2010;*

Bellmund et al., 2016; Horner et al., 2016; D. Chen et al., 2018; Maidenbaum et al., 2018; Staudigl et al., 2018; He & Brown, 2019; Bellmund et al., 2020; W. Wang & W. Wang, 2021) and the entorhinal cortex (*D. Chen et al., 2018; Maidenbaum et al., 2018; Moon et al., 2022*) in the internal, subjective representation of a person's neighbourhood, at that taking into account the target related reward (*W. Wang & W. Wang, 2021*), as well as in subjective conceptual (*Constantinescu et al., 2016*) and social metrification (*Kaplan & Friston, 2019*). However, network mechanisms of the locomotor navigational entorhinal-hippocampal system engagement into these higher psychic functions are still staying unexplained (*Ekstrom et al., 2020; Raithel & Gottfried, 2021*).

The role of each of the two entorhinal cortex part in the space metrification by the subject is ambiguous. According to the common opinion (*reviewed by C. Wang et al., 2018*), LEC/aLEC provides into the hippocampal networks information about the arrangement of the environment in the egocentric coordinates of the observer (*i.e. idiothetic information*), while, the MEC/pMEC provides information about the location of the observer in space in allocentric coordinates built on the relationships between the elements of the environment (*i.e. allothetic information*), as well as about the current motor activity and its target. Nevertheless, the role of the LEC even in the context of this scheme seems broader (*Kuruvilla, Wilson & Ainge, 2020*), both parts of the entorhinal cortex are involved in the processing of allocentric information (*Shine, Valdés-Herrera, Tempelmann & Wolbers, 2019*), and the MEK, in turn, plays a key role in both types of navigational metrification (*Save & Sargolini, 2017*). In general, some authors (*Connor & Knierim, 2017*) tend to consider MEC as the basis of exactly idiothetic navigational metrification (*see also Campbell & Giocomo, 2018*), and LEK — as allothetic (*see Vandrey, Duncan & Ainge, 2021*). Somewhat similar conclusions can be drawn based on the data of X. Chen, Vieweg and Wolbers (*2019*).

In the context of another paradigm, information about the object (*what?*) is processed by the LEC, information about the place (*where?*) — by the MEK (*Connor & Knierim, 2017; Nilssen et al., 2019; Fernández-Ruiz et al., 2021*), though

the information processing networks for these two features (*ventral and dorsal stream, respectively*) appeared to be less segregated than it had been assumed before (*Huang et al., 2021*). Naumann et al. (*2018*) state that the aLEC networks are preferentially activated in response to the demonstration of object images, while the pMEC networks — to the images of rooms and locations. According to other data (*Peng et al., 2018*), the human aLEC participates in processing of the object-associated information, pMEC — visually-associated information. There is also evidence that accurate information about the observer's position in space is formed due to LEC on the base of the data about location of the environment objects (*Vandrey et al., 2021*). And at the same time, other data indicate that navigation based on the close to the animal positional determinants does not require function of MEC and LEC at all, and navigation based on distant positional determinants is carried out with the participation of MEC (*Poitreau et al., 2021*).

1.6.2. Time

Field CA1 of the hippocampus of the mammals, and, probably, the MEC (*Salz et al., 2016*) contains neurons, whose "rosary" of individual activity bursts can represent time segments of different scales — seconds, minutes, and days (*Eichenbaum, 2017; Mau et al., 2018*). Their activity significantly depends on the MEC function (*Eichenbaum, 2017*), and the MEC, in a whole, plays significant role in memorizing (*Vo et al., 2021*) and exact reproduction (*Dias, Ferreira & Remondes, 2021*) of temporal intervals.

In its turn, temporal information about engrammed behavioral episodes can also be extracted from the LEC neurons network activity, at that in various scale — from seconds to hours (Tsao et al., 2018), possibly, even days (Bellmund, Deuker & Doeller, 2019). The LEC neurons, function of which is considerable for the engramming of temporal information, possess the property to slowly reduce activity after a sharp or gradual its increase (*ramp-like activity; Tsao et al., 2018*), which allows to obtain within the set of this cells, chains of their sequential firing, similar to the time cell chains (*Rolls & Mills, 2019*). In the same way, temporal information can be obtained through analysis of activity of the set of macaque

anterior and posterior entorhinal cortex neurons (*Bright et al., 2020*).

The shaping of the spatio-temporal map of the experienced events (*Deuker et al., 2016*), exact representation and reproduction of their temporal structure (*Bellmund et al., 2019; Montchal et al., 2019*) are performed under the leading aLEC participation. Though, mechanisms of, for example, mnestic reconstruction of the events temporal sequence remain unknown (*Bellmund, Deuker, Montijn & Doeller, 2022*).

1.6.3. Speed

The results of a number of early and recent studies (*C. Sun et al., 2015; Kropff et al., 2015; Hinman, Brandon, Climer, Chapman & Hasselmo, 2016; Ye, Witter, Moser & Moser, 2018; reviewed Tukker et al., 2022*) testify to the existence of brain neurons, activity of which closely correlates with the value of an animal linear speed — the so-called speed cells. Unlike population of such cells in hippocampus, the MEC speed cells are a rather distinct functional group (*Kropff et al., 2015*). Some MEC cells whose activity correlates with an animal movement speed are parvalbumin-positive, inhibitory neurons that project into the hippocampus (*reviewed Tukker et al., 2022*). However, in general, the composition of the MEC speed cell population and its relation to other populations of the navigation system neurons currently remain unknown (*see Tukker et al., 2022*).

1.6.4. Memory

The memory function is provided with key participation by the entorhinal-hippocampal complex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex, inferior and lateral frontal cortex parts, inferior and lateral parietal cortex parts, structures of the fornix, nucleus basalis of Meynert, amygdaloid complex, hypothalamus, nucleus accumbens, and, possible, some thalamic nuclei and the pedunculopontine nucleus (*reviewed by Khan, D'Agostino, Calnan, Lee & Aronson, 2019*).

The entorhinal-hippocampal complex is well known for its participation in the engramming of current information (*Kelley, Evans & Kelley, 2018; Rolls, 2018*), at that, not only spatial (*Suthana et al., 2012*), but also integral one, i.e. whole episodes, with their temporal, spatial, so-

cial and other attributes (*Sugar & Moser, 2019; Bellmund, Polti, & Doeller, 2020*). As mentioned before, LEC/aLEC is regarded as one of the nodes of episodic (*Bellmund, Polti, & Doeller, 2020; Takehara-Nishiuchi, 2022*) and temporal (*Deuker et al., 2016; Tsao et al., 2018; Bellmund et al., 2019; Montchal et al., 2019; Bellmund, Polti, & Doeller, 2020*) memory. The entorhinal cortex also plays significant role in engramming of the affective-emotional information, particularly, under participation of the pyramidal and stellate neurons of the MEC layer II (*Kitamura, 2017*).

It should be mentioned also that the entorhinal-hippocampal complex participates in transformation of the primarily engrammed information into the semantically linked, conceptual, and therefore long-term retained information (*Dandolo & Schwabe, 2018; see also Sekeres, Winocur & Moscovitch, 2018*).

1.7. Entorhinal Cortex and Alzheimer's disease

The role of the entorhinal cortex, LEC in particular, in brain pathology has been most substantially studied regarding the Alzheimer's disease (*Kobro-Flatmoen et al., 2021; Olajide, Suvanto & Chapman, 2021; Tran, Speck, Gallagher & Bakker, 2022*), but it is not limit with this disease only (*e.g., see Braden & Riecken, 2019*). For a long time, the most significant decrease in neuron number under the Alzheimer was revealed only in the hippocampus, particularly, in field CA1, then — also in the hilus of the dentate gyrus, in the subiculum, and in the layers II and V of the entorhinal cortex (*Beall & Lewis, 1992; Solodkin & van Hoesen, 1996; van Hoesen, Augustinack, Dierking, Redman & Thangavel, 2000; R. Insausti & Amaral, 2012*) and in the perirhinal cortex (*van Hoesen et al., 2000*). A decrease in the entorhinal cortex volume under the Alzheimer's disease is also revealed by the life-time MRI studies (*Wisse et al., 2014*), and its key role in the disorder pathogenesis is confirmed by the comparative regional analysis of the genetic expression in the cerebral cortex (*Gryglewski et al., 2022*).

In a human, with aging, the area of the entorhinal tuberosity and average number of neurons in ordinary island/protuberance significantly decreases, and entorhinal cortex layer III neurons are the first to demonstrate senile accumulation

of pathological neurofilament aggregates (*Simic et al., 2005*), at that in the elderly persons with absent cognitive disorders the MRI-detected entorhinal cortex atrophy correlates with presence of the β-amyloid accumulations (*Nosheny et al., 2019*). The human entorhinal cortex can also accumulate the τ-protein neurofibrillary tangles even in the pre-clinical phase of Alzheimer's disease (*Llamas-Rodríguez et al., 2022*), though for some variants of this pathology, accumulation of the τ-protein in typical brain regions is not pathognomonic (*Singleton et al., 2021*).

A significant vulnerability of the entorhinal cortex layer II neurons was proven in the model of Alzheimer's disease (*Yang et al., 2018*), and rapid age-related disturbances of this entorhinal cortex layer projection were described in intact animals (*Amani et al., 2021*). There is an assumption that the LEC neurons are affected under the Alzheimer's disease retrogradely, due to the action of the certain dentate gyrus pathological factors (*Young, 2020*). A number of studies reveal significant age-related decline in persistent firing ability of the LEC layer III pyramidal neurons, which cause deficits in temporary associative memory and learning (*Lin, Sherathiya, Oh & Disterhoft, 2020; Lin, Oh & Disterhoft, 2022*).

And yet, the conclusion about Alzheimer's disease-dependent reduction in the entorhinal cortex neuronal population is called into question by the available, albeit far from complete data on the age-related dynamics of this neuron population in relatively intact individuals.

Thus, Heinsen et al. (*1994*) state a negative correlation between the number of the entorhinal cortex layer II neurons of each hemisphere and the individual's age, so that when comparing the averaged data for persons aged 20 and 85 years, they note the loss of up to 27 % of the neurons of the considered layer. Simic et al. (*2005*) define this index for the age sample of 32–83 years at the level of 44 %. Kordower et al. (*2001*) registered loss of 64 % of the entorhinal cortex layer II neurons, in patients of 80–97 years old, under mild cognitive deficits, while under the Alzheimer's disease the value was 58 %. Price et al. (*2001, as cited in R. Insausti & Amaral, 2012*) state the 0.7 % annual age decrease of the entorhinal cortex neurons population in people with mild,

preclinical Alzheimer's disease, at that the 1.2 % level of decrease was revealed for layer II neuronal population. According to R. Insausti, A.M. Insausti, Sobreviela, Salinas and Martínez-Peñuela (*1998*), as cited in R. Insausti and Amaral (*2012*), age-related decrease of the entorhinal cortex area in the interval 12–110 years reached 4 %. While, Gómez-Isla et al. (*1996*) did not detect the left entorhinal cortex layer II neuron loss in individuals with no signs of dementia during the age range from 60 to 89 years, at all.

1.8. Betz Cortical Glomeruli
1.8.1. Glomerula corticalia

A neuromorphological description, presented below, is nowadays the first cytoarchitectonic evidence about the entorhinal cortex modular organization, i.e. existence of entorhinal islands: «*The end of the Ammon and the entire end of the temporal lobe (polus temporalis) have the peculiarity that in them the pyramids of the third layer, in addition to their own place, is also placed directly under the first layer. Here they are arranged quite peculiarly in large round heaps, located at a considerable distance from one another. The pyramidal cells of these heaps are arranged in a variety of di- rections to each other, directions, which are sim- ilar with the directions of the rows of threads in a ball, so I want to name them glomeruli of the cortex (glomerula corticalia).*». This is a part of the paper by Volodymyr Betz, completed by him on November 15, 1880, and published in Russian in 1882 (*translation — ours, with maximum ob- servance of the author's vocabulary and style pe- culiarities*). The Russian-language version of this article is almost identical to the world-famous German version of 1881 (*fig. 2*). Here is quote from the relevant part: "*Das Ende der Ammonswindung und das ganze Ende des Schläfenlappens (Polus temporalis) besitzen die Eigentümlichkeit, dass in ihnen die Pyramidenzellen der dritten Schicht auch noch unmittelbar unter der ersten Schicht anzutreffen sind. Hier lagern sie sich ganz eigentümlich in Form grofser, runder Haufen, die durch bedeutende Zwischenräume von einander geschieden sind. Die Pyramidenzellen dieser Haufen selbst sind ganz eigentümlich gegen einander gerichtet und erinnern an Garnknäule, weshalb ich sie „Glomeruli cor-*

ticales" benannt habe." (*Betz, 1881, N. 12, p. 211*). In the same work, we also find another, hitherto unnoticed by commentators, fragment, which reinforces Betz' priority in description of the entorhinal cortex modular organization: «*The Ammon gyrus of this brain* [referring to the brain of Mottè, or Motey, who suffered from idiocy — V.M.] *represents a very strongly developed substantia reticularis alba, which, especially on the inferior part of the gyrus, represents the appearance of the fish caviar grains located next to each other.*» (*Betz, 1882; translation is ours, with maximum observance of the author's style — V.M.*). The German version is identical: "*Die Ammonswindung dieses Gehirns hat eine sehr stark entwickelte Substantia reticularis alba, welche namentlich an dem unteren Teile der Windung das Aussehen von dicht neben einander gelagerten Fischlaichkörnern hat.*" (*Betz, 1881, N. 13, p. 232*). The fact that the author is fully aware of the unordinarity of his own cytoarchitectonic observation is demonstrated by a fragment from the introductory part of the article, which states the following: «*Regarding the peculiar structure specificity following cortex parts are differentiated: the anterior central gyrus* [precentral gyrus — V.M.]*, cingulate gyrus (gyrus cinguli), Ammon gyrus, third frontal* [gyrus — V.M.]*, paracentral lobule, lingual lobule (gyrus lingualis), terminal lobule (lobulus extremus) and **the end of the temporal lobe (polus temporalis)**.*» (*Betz, 1882; translation is ours, with maximum observance of the author's style; highlighting is ours — V.M.*). The German version is almost identical: «*Ganz besonders charakteristisch ist der Bau folgender Rinde bezirke: der vorderen Central windung, der bogenförmigen Windung (Gyrus cinguli), der Ammonswindung, der dritten Stirnwindung, des Lobulus paracentralis, des Gyrus lingualis, des Lobulus extremus und **das untere** Ende des Polus temporalis.*» (*Betz, 1881, N. 11, p. 195; the Russian and German versions differ by the word we highlighted, the meaning of which is 'the lower'*). After difficult searches, we managed to find among Betz's collection of preparations precisely those that, in our opinion, contain the morphological material described in the above quotations (*fig. 3–5*).

Fig. 2. Three consecutive March issues of the German scientific and medical periodical "Centralblatt für die medicinischen Wissenschaften" ("Central journal for the medical sciences", Berlin) in which Betz's article (*1881*) was printed in three parts. In the first two numbers (*N. 11 and N. 12*) the relevant parts of Betz's work are placed first, in the third of the considered numbers (*N. 13*) the final part of Betz's work is placed fourth. Source of the electronic file of the edition number binder for 1881: https://archive.org/details/bub_gb_acADAAAAYAAJ/page/192/mode/2up
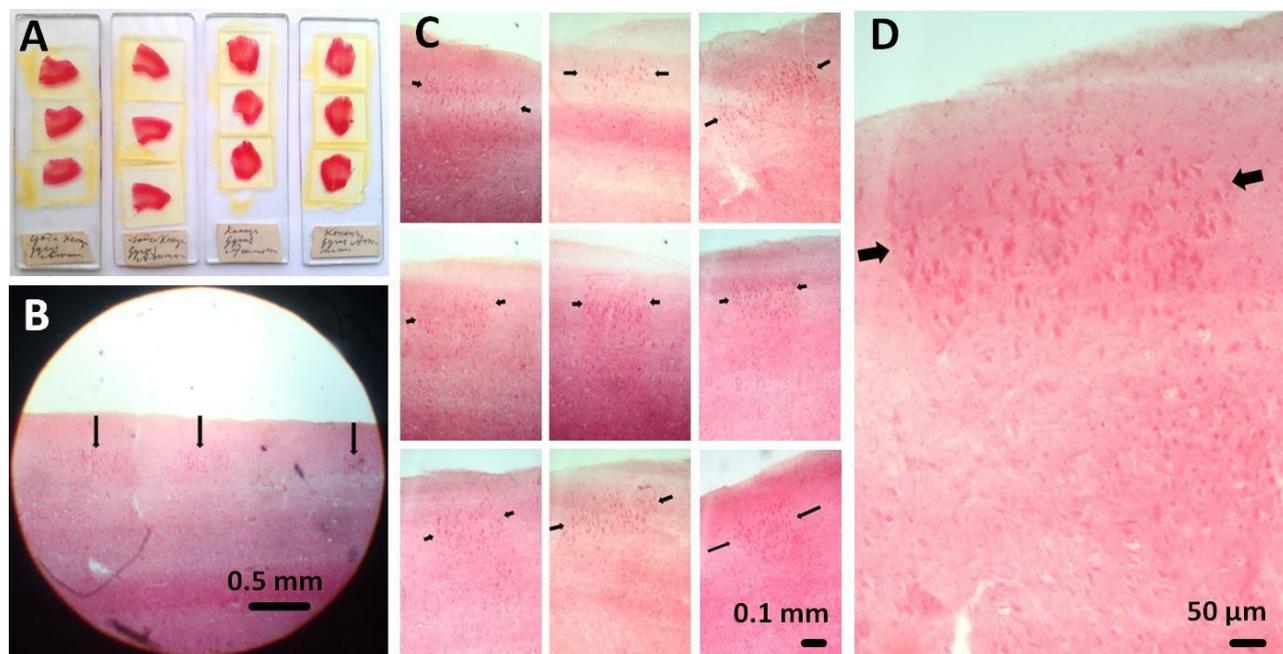
Fig. 3. *Glomerula corticalia* on Betz's authentic preparations.

A — four histological preparations with the carmine-stained «*end of Ammon's gyrus*» sections. Betz's own handwritten inscriptions (*in our reconstruction*): on the two preparations located on the left — «*posteriorly [from] the End of gyrus Amm[onis]*», on the two preparations located on the right — «*End of the*

gyrus Amm[onis]»; the inflexion of the word «*Amm[onis]*» in both cases is illegible. The wording of these signatures exactly corresponds to the terminology of the above-cited place of the article by Betz (*1882*), where the islands of the entorhinal cortex, i.e. *glomerula corticalia*, were first described. This leaves no doubt that the source of this description was at least these four preparations from Betz's collection given here.

B — view of a typical part of the cortex histological section, available on one of the four Betz's preparations we examined; arrows indicate entorhinal islands (*in our deep convinsion*).

C, D — variants of the entorhinal islands (*in our deep convinsion*), which we found in our deep convinsion on the same four Betz's preparations, at different magnifications (*the boundaries of the islands are marked horizontally with black arrows*)
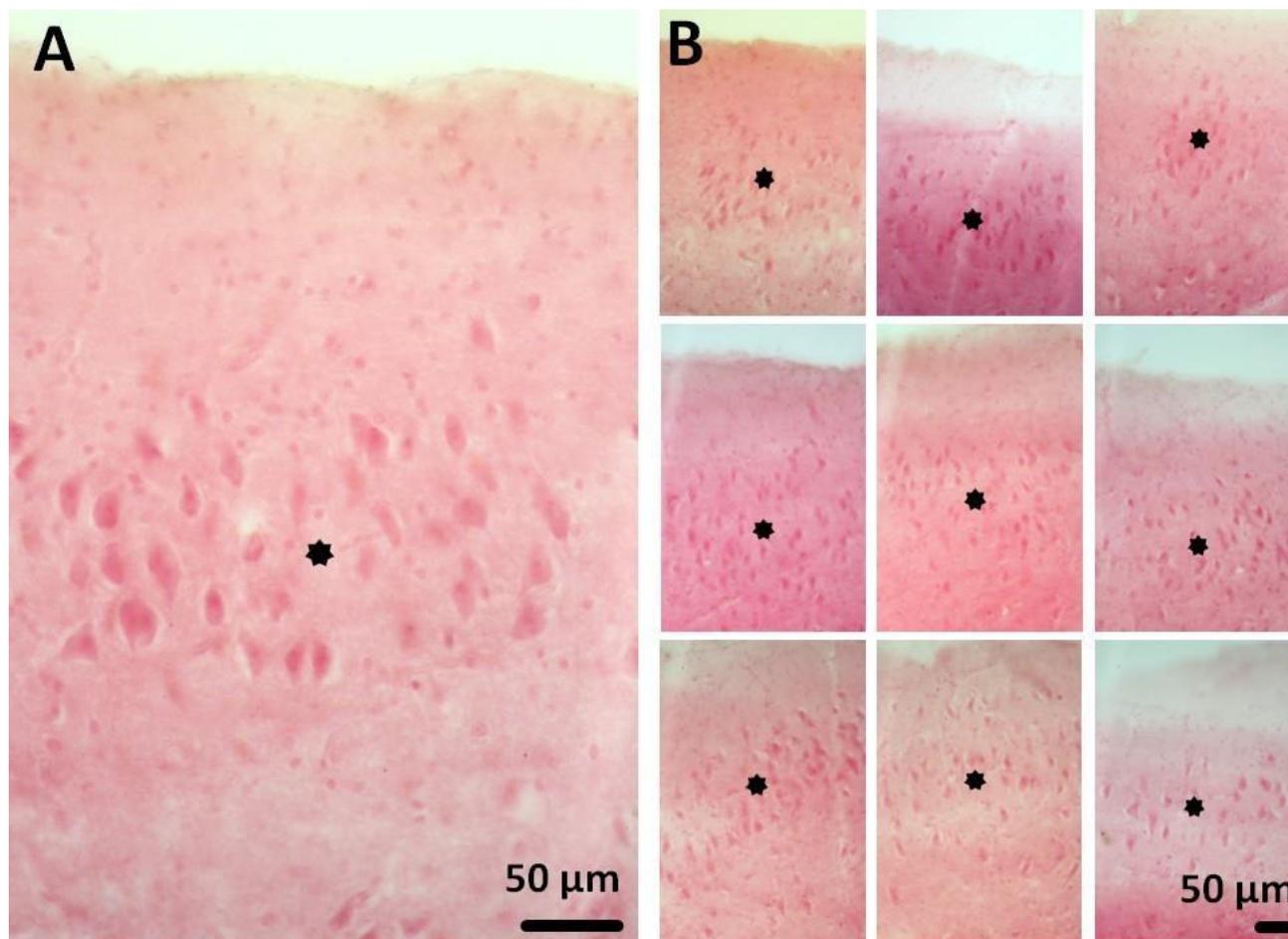
Fig. 4. Variants of the entorhinal islands (*in our deep convinsion*), which we found on the Betz's preparations (*fig. 3 A*), at different magnifications (**A, B**). Carmine-staining in our deep convinsion. In each photomicrograph, the conventional center of the entorhinal island is marked with a black asteriks

Betz's priority regarding the description of the Ammon's horn cortex cytoarchitectonics has been recognized by Ramon y Cajal (*1988, work of 1901–1902, p. 294–295*): «*The structure of the hippocampal gyrus in man and that of the piriform lobule in animals have been little studied. In general, the authors have distinguished in the hippocampal gyrus two regions or segments: the subiculum, or portion adjacent to Ammon's horn,* recognizable by showing a plexiform layer furrowed by thick bundles of white matter; and the principal portion, distant from [Ammon's] horn, in which an organization almost identical to that of the other [cerebral] gyri has been supposed. However, some authors, among whom **we must cite Betz**, Obersteiner, Dejerine, Hammarberg, and especially Calleja and Kölliker, have recognized some structural peculiarities exclusive to*
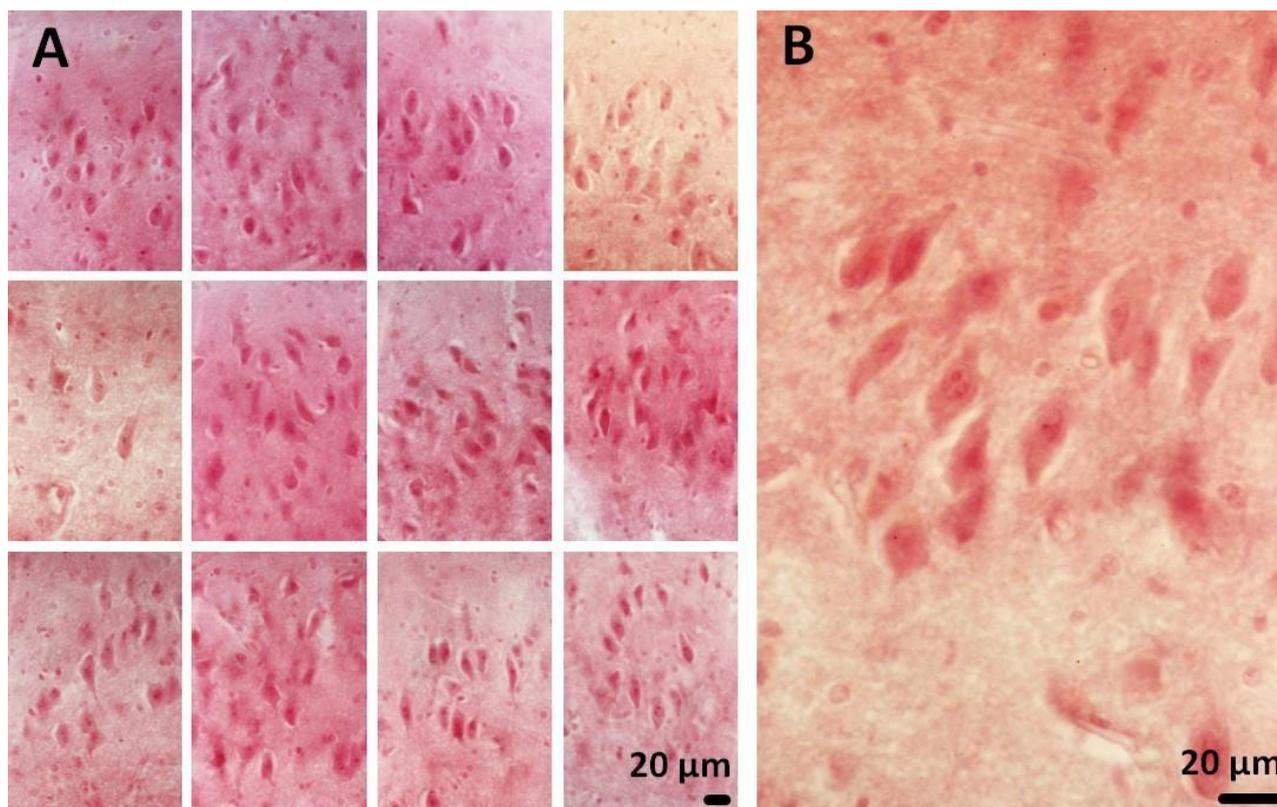
Fig. 5. Variants of the entorhinal islands (*in our deep convinsion*), which we found on the Betz's preparations (*fig. 3 A*), under strong magnification (**A**, **B**). Carmine-staining in our deep convinsion. The neuronal composition of the islands and even the cytological features of neuronal somata are well visualized (**B**)

*the piriform lobule and hippocampal gyrus. One of the typical features of the cortex of the subiculum is the presence, at the level of the small pyramids, of pleiades of cells separated by ascending bundles of white matter **which were alredy recognized by Betz,[9] who named them cortical glomeruli**. For his part, Obersteiner,[10] who studied also the structure of the subiculum ... [A]t the level of second layer, he also observed the **cellular accumulations of Betz**, as well as the bundles of white matter that separate them; ... One neurologist who dedicated more attention to the theme we are dealing with, exploring equally all the regions of the hippocampal gyrus with method of Nissl, was Hammarberg.[13] ... **In agreement with Betz and Obersteiner, he observed the small islands of the second layer and the ascending white bundles**.*" (*highlighting is ours — V.M.*).

This evidence of Ramon y Cajal is well known to specialist. Thus, Amaral, R. Insausti and Cowan (*1987*) write: «*According to Ramon and Cajal ('01, '02), Hammarberg (1895) provided the first comprehensive study of the laminar organization of the entorhinal cortex, although Betz (1881), Obersteiner (1888), and Calleja (1893) had earlier described some aspects of its structural organization.*». R. Insausti, Tuñón, Sobreviela, A.M. Insausti and Gonzalo (*1995*) in a special final part of the article, referring, most likely, to the same work of S. Ramon y Cajal, give a number of early reports on the microscopic structure of the entorhinal cortex, the first three authors in which are the analogous: Betz, Obersteiner, Calleja, and Hammanberg.

Amaral et al. (*1987*) before the brief exposition of the entorhinal cortex research history note that the thorough study of the issue were made by Stephan (*1975*) and Haug (*1976*). A close look at both of these works reveals details of the Betz's role reception in the discovery of the entorhinal islands. Thus, Haug (*1976*), describing the cytoarchitectonic features of the rat parahippocampal cortex, associates the beginning of this brain part structure study with Ramon y Cajal. Instead,

Stephan (1975) presents an original vision of a historical series of personalities who contributed most significantly to the human entorhinal cortex microstructure study. This list looks as follows (*references to relevant primary sources are given in Stephan's cited work*): Campbell (*1905*), Brodmann (*1909*), C. Vogt and O. Vogt (*1919*), von Economo and Koskinas (*1925*), Rose (*1927*), Sgonina (*1938*), and Braak (*1972*). Unexpected absence of Ramon y Cajal and Lorente de No in these list, without a doubt, is obvious to the author himself; he notes that the contribution of both morphologists is described by him separately, in point 8.11.5. Among the listed works, the author emphasizes evidence of Campbell (*1905*): he, according to Stephan (*1975, p. 666*), describes the notable near-surface clusters of the entorhinal cortex cells — «*Er gibt aber eine Beschreibung und eine sehr schone Illustration der Zell- und Faserarchitektonik von einer Gegend, die er als «as near as possible the central point of the lobule» — gemeint ist sicherlich der Gyrus parahippocampalis — beschreibt (Campbell, 1905, Plate XVII). Er gliedert die Rinde in sechs Schichten. An Besonderheiten hebt er die großen Fasermassen im Stratum moleculare hervor, und die **bemerkenswerten Zellnester an der Oberflache des Zellbandes**, die im Faserbild durch besondere Faserarmut auffallen. Die Molekularschicht ist ungewohnlich breit.*» (*highlighting is ours — V.M.*). Dwelling on this morphological peculiarity, Stephan (*1975, p. 666*) casually notes that the II layer of the entorhinal cortex contains two types of nests — those which consist of polymorphic giant cells and those that contain significant number of small pyramidal cells: «*Die zweite Schicht enthalt zwei Typen von Zellnestern. Einmal solche aus «polymorphen Riesenzellen» (CAJAL) und solche aus kleinen Pyramidenzellen[483]). Die großen Zellen haben beim Menschen einen mittleren Durchmesser von 28 mkm und sind bevorzugt sternformig. Der Kern ist klein und liegt im Zentrum des Zellkörpers. Die kleinzelligen Nester enthalten viele sehr kleine Zellen.*». At this point the author gives a key for us footnote (*at number 483*), in which he states that the cellular nests mentioned, besides Ramon y Cajal, according to Campbell, are described also by Hammarberg and Flechsig; however, Stephan continues,

according to von Economo and Koskinas, "*Betz may have been the first to describe the 'glomeruli corticales' of the 'Ammon gyrus anterior part and the temporal pole'*": «*Diese charakteristischen Zellnester sind neben CAJAL auch von HAMMARBERG und FLECHSIG beschrieben worden (CAMPBELL, 1905, S. 179). Nach ECONOMO u. KOSKINAS (1925) hat möglicherweise BETZ die «glomeruli corticales» des «vorderen Teils der Ammonswindung und des Temporalpols» erstmals beschrieben.*» (*H. Stephan, 1975, p. 666, footnote 483*). The phraseological and lexical closeness of Betz's indirect quotation given by Stephan (*1975*) with the relevant fragment of its Russian and German counterpart (*see above*) leaves no doubt that von Economo and Koskinas considered Betz to be probably the first to testify the existence of entorhinal cortex layer II neurons clusters, naming them "*glomeruli of the cortex*".

Knowing all this, it is not difficult to guess where the term "*entorhinal glomeruli*" appeared and was used throughout the 20th century in the literature devoted to the microstructure of the entorhinal cortex. For example, in the English reprint of von Economo's work, it is the term "*glomeruli*" is used to denote the islands of the entorhinal and adjacent areas of the cortex (*von Economo, 2009, p. 150–169*). Unfortunately, in the cited reprint of von Economo's work has not preserved information about the etymology of the term, which, as just mentioned, according to Stephan (*1975*), was present in the 1925 edition. Altschul (*1933*), although with reservations, uses the same lexeme for description of the island structures of the mammalian presubiculum. Solodkin and van Hoesen (*1996*), referring to a number of sources, call the entorhinal islands «*concentric patches that create the impression of glomeruli*». A similar historical name of the entorhinal islands is also mentioned by Simic et al. (*2005*).

It should be noted that the tradition of calling the entorhinal glomeruli as islands (*and islets*) dates back to Ramon y Cajal, in any case, in his work devoted to the olfactory cortex of humans and mammals, such terms (*islands, islets*) in relation to the structures under consideration are found everywhere (*Ramon y Cajal, 1988, work of 1901–1902, pp. 295-315*). Solodkin and van Hoesen (*1996*) once used the term "*clumps*" to

denote entorhinal islands, R. Insausti et al. (*2017*) call the clusters of the II layer of the presubiculum in this way. Finally, there is precedent for using the term "*nests*" (van Hoesen et al., 2000) to refer to entorhinal islands.

We also note that van Hoesen et al. (*2000*), citing the work of Bielschowsky (*1928*) in the context of history of the Alzheimer's disease pathomorphological signs elucidation, evidence to his use of the term "*islands of Cajal*" in relation to the cell clusters of the subiculum outer layer. van Hoesen et al. (*2000*) immediately correct Bielschowsky, recalling that Ramon y Cajal described such peculiarity of cytoarchitectonic precisely in relation to the entorhinal cortex, and the co-inclusion of the subiculum in its boundaries is doubtful. However, in our opinion, a completely different circumstance is doubtful in this situation — the use of the eponym in relation to the cell clusters of the entorhinal cortex outer layer without taking into account Betz's pioneering observation.

1.8.2. Entorhinal Tuberosity and *Substantia Reticularis Alba*

As it was mentioned before, the layer II neuronal glomeruli, or islands represent a unique differential sign of the entorhinal cortex, which has a macroscopic correlate (*Solodkin & van Hoesen, 1996, p. 620; van Hoesen et al., 2000,* p. *259; Simic et al., 2005, p. 911*): in the intermediate and caudal regions of the entorhinal cortex, they form the tuberosity of the surface (*fig. 1 C*), described as a collection of "*verrucae hippocampi*" (*R. Insausti et al., 1995*), or "*warts*" (*R. Insausti et al., 1995; R. Insausti & Amaral, 2012*), "*bumps*" (*R. Insausti et al., 1995*) or even "*wart-like bumps*" (*Witter, Doan, et al., 2017*). Most likely, the grayish spots often visible to the naked eye are associated with the "*verrucae hippocampi*" — areas where the entorhinal islands can be seen through the surface of the cortex (*Hevner & Wong-Riley, 1992, p. 455 and fig. 3*).

In our opinion, the emergence of the term "*verrucae*" of the human parahippocampal gyrus anterior part is most comprehensively described by van Hoesen et al. (*2000*). According to them, Retzius (*1896*) commented on this morphological peculiarity of the anterior medial temporal region surface, comparing it to the skin surface of some amphibians. Klingler (*1948*), as noted by van Hoesen et al. (*2000*), subsequently generalized, detailed and deepened the observations of Retzius. The priority of Retzius in the description of entorhinal tuberosity, i.e. entorhinal *verrucae* is also recognized by other authors (*Simic et al., 2005; Witter, Doan et al. 2017*). However, in both quoted versions of Betz' work (*1881, 1882*), completed by him on 15th November 1880, we find an earlier and, in our opinion, an accurate and exquisite description of this morphological phenomenon: «*The Ammon gyrus of this brain* [referring to the brain of Motey, who suffered from idiocy — V.M.] *represents a very strongly developed substantia reticularis alba, which,* **especially on the inferior part of the gyrus, represents the appearance of the fish caviar grains located next to each other**.» (*Betz, 1882; translation — ours, with maximum observance of the author's style; highlighting is ours — V.M.*).

Also notable in this quote is Betz's mention of another macroscopic feature of the entorhinal region. When examining the surface of the intact human entorhinal cortex between the dark spots, which correspond to the visible through the thin surface entorhinal islands, one can observe the white matter (*R. Insausti & Amaral, 2012; fig. 1 D*), which probably contains associative fibers from other areas of the cortex (*van Hoesen et al., 2000*). This macroscopic feature was first described, according to van Hoesen et al. (*2000*), in the work of Arnold (*1851*), so that it is now known as the *substantia reticularis alba* of Arnold. «*At the transition of gyrus cinguli to gyrus ammonii ... a white layer of longitudinal fibers of gyrus cinguli passes on the surface of the entire gyrus above it and, gradually increasing, forms the so-called white granular substance of the ammon's horn (substantia reticularis alba) and, finally, wraps into the creature of the ammon's horn, where it is described by Meinert under the incorrect name of a granular leaf (Kernblatt) in the form of a white nonthrough septum.*» (*Betz, 1882; translation — ours, with maximum observance of the author's style, V.M.*). The German version is very similar: "*An der Uebergnngsstelle des Gyrus cinguli in den Gyrus Ammonii ... und die weifse Schicht der Längsfasern des Gyrus cinguli verläuft längs der Oberfläche des Ammon-*

shorns und bildet, immer gröfser werdend, die sog. weifse Kernsubstanz desselben (Substantia reticularis alba); dann biegt sie in die Substanz des Ammonshorns, selbst um, wo sie als weifse unvollkommene Scheidewand von Meinert unter dem unrichtigen Namen „Kernblatt» beschrieben wurde." (*Betz, 1881, N. 12, p. 210*).

1.8.3. Entorhinal Cortex Clusters as the first Evidence of Modular Brain Organization

One of the most widespread current concepts of neurobiology is the idea of a neural networks modular organization. There is an opinion (*Naumann et al., 2018*) that the entorhinal cortex neuronal composition clustering is perhaps the first historical evidence in its favor. However, the formulation of this idea is difficult to imagine outside the neurohistological context, as evidenced by at least the history of the cortical column concept. Therefore, the appeal of Naumann et al. (*2018*) to the macroscopic observations of Arnold (*1838*) and Retzius (*1896*) as the first evidence in favor of the modular organization of the brain is doubtful. Instead, Betz's observations discussed above, together with other neurohistological non-ordinaries described by him, which we will describe in one of the following publications, can be confidently considered the first arguments in favor of this currently widespread neurobiological concept.

Conclusion

Having reviewed modern notion about the structure and functions of the entorhinal cortex, we can affirm the unique and fundamental significance of Betz's pioneering observation regarding layer II neuronal islands of this cortex part, named by him "*glomerula corticalia*". There is no doubt that in the foreseeable future we will obtain information about entorhinal islands neurons' function, the reason and meaning of these cells such clustering. However, today, a leading role of Volodymyr Betz in this cytoarchitectonic phenomenon discovery is already evident.

Conflict of interest

The authors declare no conflict of interest.

Consent for publication

All authors have read the text of the manuscript and given their consent for its publication.

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П'ять відкриттів Володимира Беца.
Частина перша. Бец і острови енторінальної кори

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Анотація: у серії публікацій, котру відкриває ця стаття, ми розглядаємо п'ять фундаментальних нейроморфологічних спостережень нашого співвітчизника, класика світової нейронауки Володимра Беца. Для чотирьох із них ми вперше демонструємо статус відкриттів, для іншого одного — гігантських пірамідних нейронів рухової кори — попри повсюдне і давнє його визнання, розкриваємо обмеженість сучасних знань і уявлень. Два із згаданих спостережень — гігантські веретеноподібні нейрони поясної й острівцевої кори і острови енторінальної кори — наданий час відомі лише вузькому колу фахівців; на решту два, острови Калеха і ознаки колонкової організації кори — ми звертаємо увагу вперше. У цій, початковій частині циклу, розкриваючи сучасні уявлення про будову і функції енторінальної кори, ми демонструємо вагу першоспостереження Бецом непересічних нейронних кластерів, відомих зараз як енторінальні острови, доводимо факт визнання його історичного пріоритету у описанні цих дивовижних структур мозку.

Ключові слова: історія медицини, нейронауки, енторінальна кора, клітини решітки, епізодична пам'ять, сприйняття часу, хвороба Альцгеймера.