DOI: 10.31088/CEM2025.14.5.69-77

Comparative analysis of cortical maturation in sulci and gyri of the visual cortex during human late prenatal and postnatal periods

O.S. Godovalova, A.E. Proshchina, A.S. Kharlamova, Yu.S. Krivova, S.V. Saveliev

Avtsyn Research Institute of Human Morphology of FSBSI "Petrovsky National Research Center of Surgery", Moscow, Russia

Abstract. *Introduction*. The formation and maturation of the cortical plate in the sulci and gyri of the human brain are incompletely understood. To evaluate the maturation pattern of the gyrified cortex, the distribution of immunohistochemical markers for synaptic activity and mature neurons in the human visual cortex was investigated during the late fetal and postnatal periods.
Materials and methods. We analyzed 14 human post-mortem brain samples. The distribution of GAD65/67, GAT-1, and NeuN in sulcal and gyral regions and sulcal banks was examined using immunohistochemistry.
Results. Cortical maturation proceeds in clusters, representing second-order functional neural assemblies. The cortical regions of sulcal banks and gyri mature earlier followed by maturation of the cortex within the sulci.
Conclusion. The gyrified cortex exhibits asynchronous maturation with the regions at the boundaries of sulci and gyri reaching maturity earlier than sulcal regions. There is a complex interplay between gyrification and cortical maturation, indicating a strong link between the structural organization of the cortex and its functional development.

Keywords: visual field, cerebral maturation, gyrification, sulci, gyri, human brain development, GAD65/67, GAT-1, NeuN

Corresponding author: Olga S. Godovalova. E-mail: godovalova.brain@gmail.com

For citation: Godovalova O.S., Proshchina A.E., Kharlamova A.S., Krivova Yu.S., Saveliev S.V. Comparative analysis of cortical maturation in sulci and gyri of the visual cortex during human late prenatal and postnatal periods. Clin. exp. morphology. 2025;14(5):69–77. DOI: 10.31088/CEM2025.14.5.69-77.

Funding. The study was carried out within the framework of State Assignment to Avtsyn Research Institute of Human Morphology of FSBSI "Petrovsky National Research Centre of Surgery" (No. FURG-2025-0031).

Received 22.04.2025. **Received in revised form** 02.06.2025. **Accepted** 27.06.2025.

УДК: 611.81.013

Сравнительный анализ созревания борозд и извилин зрительной коры в поздний пренатальный и постнатальный период развития человека

О.С. Годовалова, А.Е. Прощина, А.С. Харламова, Ю.С. Кривова, С.В. Савельев

Научно-исследовательский институт морфологии человека имени академика А.П. Авцына ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия

Резюме. *Введение.* Процессы формирования и созревания корковой пластинки внутри борозд и извилин головного мозга человека остаются не до конца изученной областью нейронауки. Для оценки характера созревания гирифицированной коры проведено иммуногистохимическое исследование распределения маркеров синаптической активности и маркера зрелых нейронов в зрительной коре головного мозга в позднефетальном и постнатальном периоде.
Материалы и методы. Проанализировали 14 аутопсийных образцов головного мозга человека. Проведено иммуногистохимическое окрашивание с антителами GAD65/67, GAT-1, NeuN с последующим сравнением распределения перечисленных маркеров в области борозд, губ борозд и извилин затылочной доли головного мозга.
Результаты. Установлено, что созревание коры протекает кластерами – функциональными нейронными объединениями второго порядка. Было показано более ранее созревание коры в области губ борозд и извилин и более позднее внутри борозд.

Заключение. Продемонстрировано асинхронное созревание гирифицированной коры, при этом области на границах борозд и извилин созревали раньше, чем области борозд. Подчеркнуто сложное взаимодействие между гирификацией и созреванием коры, указывающее на прочную связь между структурной организацией коры и ее функциональным развитием.

Ключевые слова: зрительное поле, созревание головного мозга, гирификация, борозды, извилины, развитие головного мозга человека, GAD65/67, GAT-1, NeuN

Для корреспонденции: Ольга Сергеевна Годовалова. E-mail: godovalova.brain@gmail.com

Для цитирования: Годовалова О.С., Прощина А.Е., Харламова А.С., Кривова Ю.С., Савельев С.В. Сравнительный анализ созревания борозд и извилин зрительной коры в поздний пренатальный и постнатальный период развития человека. Клин. эксп. морфология. 2025;14(5):69–77. DOI: 10.31088/CEM2025.14.5.69-77.

Финансирование. Исследование выполнено в рамках государственного задания Научно-исследовательского института морфологии человека имени академика А.П. Авцына ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского» (№ FURG-2025-0031).

Статья поступила 22.04.2025. **Получена после рецензирования** 02.06.2025. **Принята в печать** 27.06.2025.

Introduction

Studies on the maturation of the human neocortex represent an important area of neurobiological research. The gray matter is crucial for integrating sensory information, memory formation, and higher-order thinking skills. Understanding the mechanisms of cerebral cortex maturation may help identify the causes of neurological and psychiatric disorders such as autism spectrum disorder and schizophrenia. Investigations into age-related and individual differences in cortical maturation could contribute to developing effective diagnostic and intervention strategies for cognitive and emotional development.

A key characteristic of human neocortex development is its pronounced gyrification. Broader cortical maturation and the processes underlying sulcus and gyrus formation remain poorly understood in neuroscience.

Our previous findings indicate that cortical plate formation progresses more slowly within sulci than within gyri of the same cytoarchitectonic field during early and middle fetal periods [1]. The study focused on the visual cortex, particularly the calcarine sulcus (primary visual field 17) and parieto-occipital sulcus (secondary visual field 18). This region was selected due to its accelerated synaptogenesis observed within the visual cortex [2, 3] and stable association between these sulci and their respective cytoarchitectonic fields [4].

Neuronal maturity markers include synaptic activity markers, NeuN, GAD65/67, and GAT-1.

Glutamate decarboxylase (GAD), an enzyme responsible for synthesizing γ-aminobutyric acid (GABA), is the most prevalent inhibitory neurotransmitter in the central nervous system (CNS) of higher vertebrates [5]. GAD exists in two isoforms—GAD65 and GAD67, named for their molecular weights, which function synchronously to produce and regulate physiological GABA levels [5].

The GABA transporter 1 (GAT-1) is the primary GABA transporter in the brain that plays a crucial role in modulating GABAergic transmission. It is predominantly found in axon terminals forming symmetrical synapses and astrocytic processes [6].

NeuN is a marker for most postmitotic neuroblasts and mature neurons in vertebrate animals [7].

To assess cortical maturity in the sulcus, gyrus, and sulcal banks of the visual cortex, we analyzed the distribution of GAD65/67, NeuN, and GAT-1 using immunohistochemistry.

Materials and methods

This study used autopsy specimens from the archival collection of the Laboratory of Nervous System Development of Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Center of Surgery.” The study was approved by the local Ethics Committee (No. 33(9), February 7, 2022). Fourteen post-mortem human brain samples were analyzed: (1) six late-fetal period specimens (29–40 gestational weeks); (2) six pediatric samples (1 day–4 years); and (3) two adult samples (48 and 70 years). Gestational age was calculated from the last menstrual period, verified by ultrasound examination, and supplemented with anthropometric parameters (weight/height and crown-rump length) [8]. Our analysis included samples without clinical records indicating chromosomal anomalies or CNS pathology. Samples for immunohistochemical analysis were selected after histological assessment of material preservation. We excluded samples with hemorrhages, necrosis, or signs of post-mortem autolysis, as well as samples with prolonged storage in formalin due to the potential impact on immunoreactivity distribution. The data on human occipital lobe formation at earlier developmental stages are available on the Human Brain Development Atlas project website at https://brainmorphology.science [9, 10].

Histological preparation and immunohistochemistry

All brain samples underwent histological processing. Depending on the fetal age, we examined either the whole brain or a region of the medial wall of the hemisphere encompassing the calcarine sulcus (*sulcus calcarinus,* Cas) and parieto-occipital sulcus (*sulcus parietooccipi-*

talis, Pos). Samples were immersion-fixed in either 10% neutral buffered formalin (pH 7.0–7.4) or Bouin's solution, followed by dehydration in graded ethanol solutions and dioxane. Tissues were then paraffin-embedded and sectioned at 10-μm thickness. Sections were stained with classic histological cresyl violet (Nissl stain) for cytoarchitectural analysis and mounted on Superfrost Plus slides (Thermo Fisher Scientific, USA) and stored at 4°C. Immunohistochemical analysis was performed using primary antibodies targeting nervous system antigens: NeuN (Millipore, RRID: AB_2298772, Germany) at a dilution of 1:100, GAT-1 (Millipore, RRID: AB_90791, Germany) at a dilution of 1:100, and GAD65/67 (Thermo Fisher Scientific, RRID: AB_930942, USA) at a dilution of 1:50. For immunohistochemical labeling, sections were deparaffinized, rehydrated, boiled in citrate buffer (pH 6.0; DiaGene, Russia) for 10 min, and incubated with primary antibodies diluted in 0.01 M phosphate-buffered saline (PBS, pH 7.3–7.5; Biolot, Saint Petersburg, Russia) for 1 h at room temperature for NeuN and GAT-1 and for 18–20 h at 8°C for GAD65/67. Visualization was achieved with The Ultra Vision LP Detection System (Thermo Fisher Scientific, USA). Negative control sections were obtained by replacing the primary antibodies with PBS (0.01 M). Non-specific staining was absent in all control sections.

Statistical analysis

We analyzed all specimens under a light microscope (DM 2500; Leica Microsystems, Germany) connected to a digital camera (Lomo, Russia). Images were acquired and processed using McrA-View 7.1.1.2 software (Lomo, Russia). Measurements were performed on photomicrographs of the specimens. We scanned some specimens using a modified MEKOS-C2 complex (MEKOS, Russia) based on a Zeiss Axio Imager 1 microscope (Carl Zeiss, Germany) with a 20x objective. We analyzed 10 non-overlapping observation fields from 3–5 sections per region. The immunoreactivity coefficient was calculated using ImageJ software ver. 1.43 as the ratio of the sum of immunopositive (colored) pixels to the total number of pixels in the selected area.

For statistical analysis, we divided cases into three groups: late fetal (29–40 weeks), postnatal, and adult periods. The immunoreactivity coefficient values were compared in the cortical sulci, sulcal banks, and gyri. Statistical analysis was performed using Statistica 10 software (StatSoft, USA) employing the non-parametric Kruskal–Wallis ANOVA with post-hoc multiple comparisons of mean ranks.

Results

Distribution of NeuN immunoreactivity

In the late fetal period, NeuN-positive cells were in all layers of the cortical plate on the brain surface, both in gyri and sulcal banks (Fig. 1 A). The NeuN immunoreactivity coefficient was significantly higher in sulcal banks than in the sulci [p=0.000000] (Fig. 1 B). Within the sulci, the frequency of NeuN-positive cells gradually decreased from layer II to layer VI. Notably, NeuN-positive cells were predominantly localized in layer VI of the calcarine sulcus. The cortex within the parieto-occipital sulcus showed no specific layer in NeuN immunoreactivity.

In the postnatal period, the above-described trends in marker distribution were detected, which persisted from birth until 4 years postnatally. More intense staining was observed in the gyri cortex, where labeled neurons were found in all cortical layers. In the depth of the sulci, NeuN immunoreactivity was low in both areas 17 and 18.

A distinct pattern of NeuN-immunopositive cell distribution was observed at 10 months postnatally (Fig. 1 C, D). Within the sulcus, NeuN-immunopositive cells formed morphological and functional neural assemblies, predominantly in layer II with partial extension to layer III of the neocortex, and additional clusters in layers V and VI. These assemblies measured 250 μm in width in layer II and 210 μm in layer VI.

In adults, NeuN-positive neurons were found throughout the primary and secondary visual fields, with no difference in distribution in the gyri, sulcal banks, and sulcal depths.

Thus, we detected asynchronous maturation of NeuN immunoreactivity in the sulci and gyri, persisting until 4 years postnatally (Fig. 1 B, E, F).

Distribution of GAD65/67-immunoreactivity

In the late fetal period, a small number of GAD65/67-immunoreactive cells were observed in the cortex. Approaching birth, GAD65/67-immunoreactivity intensified, with a significantly higher coefficient being in the sulcal bank cortex compared to that in the gyri cortex and the cortex within the sulci within the same cytoarchitectonic fields (Fig. 2 A, B, C). In area 17, immunoreactivity was mainly localized in layers IVC and V–VI. Layers IVB and IVA had dense groups of neurons and revealed the structure of functional neuronal assemblies. Areas 18 and 19 showed strong immunoreactivity in layers II and upper layer III (Fig. 2 A, B, C), with occasional morphological and functional assemblies found in the lower layer III and layer IV. The width of the assemblies at layer IV averaged 190 μm.

Postnatally, the GAD65/67-immunoreactivity coefficient increased, particularly in gyri and sulcal banks (Fig. 2 D, E), with its statistically significant differences observed in the cortex of sulcal banks, gyri, and sulci (Fig. 2 F).

These findings demonstrate that GAD65/67 successfully captured transient cortical assemblies in newborns and revealed heterogeneity of cortical maturation in sulci, gyri, and sulcal banks.

Distribution of GAT-1 immunoreactivity

In the late fetal period, GAT-1-immunopositive fibers were distributed across the entire hemisphere wall, mainly

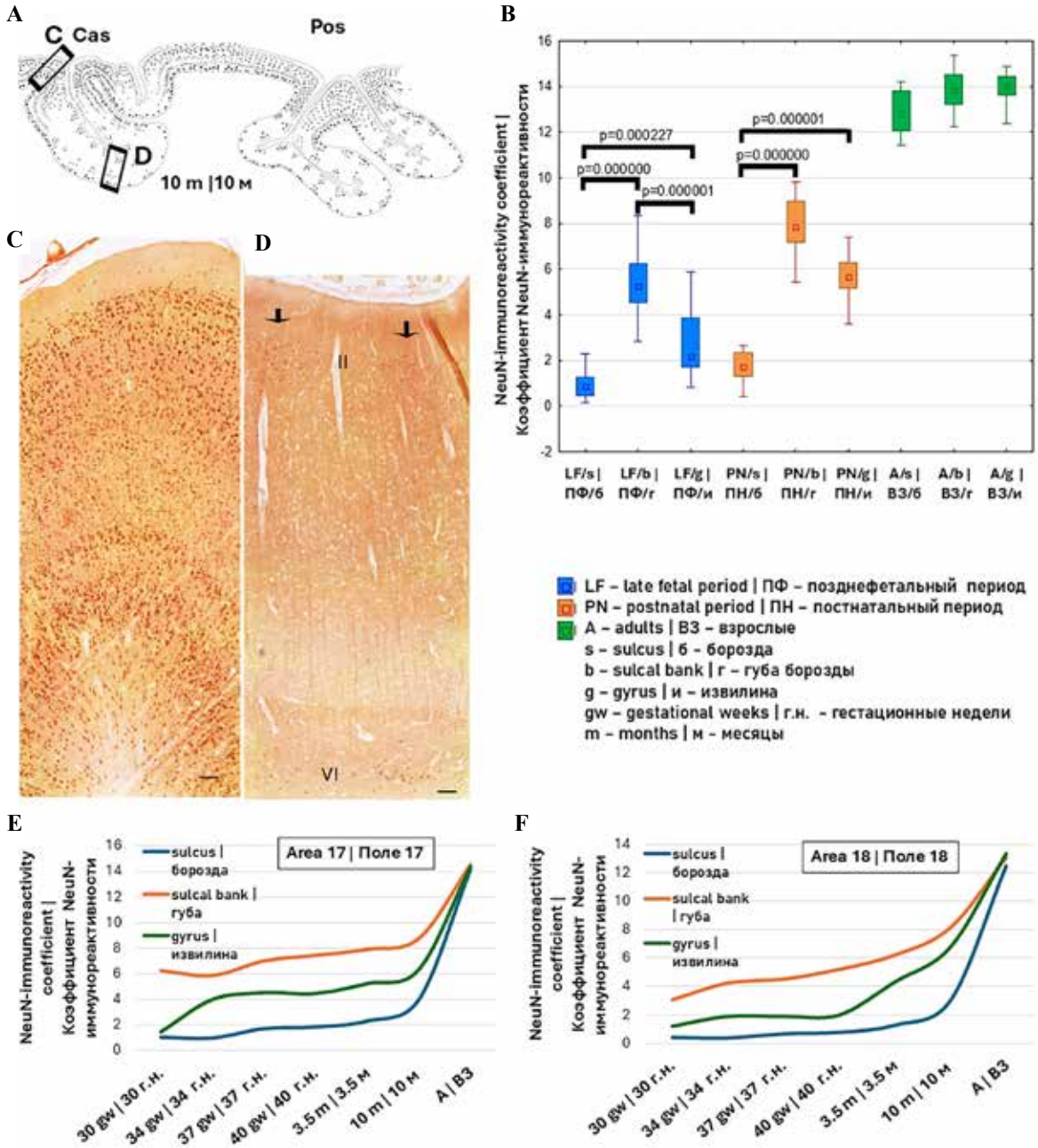

Fig.1. A – the distribution of NeuN-immunoreactive cells in the occipital cortical plate, 10-month-old infant. B – boxplots and multiple comparisons for the NeuN-immunoreactivity coefficient in the cortical plate of the occipital lobe at three locations: sulcus, sulcal bank, and gyrus, areas 17 (calcarine sulcus) and 18 (parieto-occipital sulcus). Comparable periods: late fetal period (LF), postnatal period (PN), adults (A). Significant differences between locations are marked by brackets. C – NeuN-immunohistochemical staining, a region of the cortical plate at the sulcal bank of the calcarine sulcus, area 17, 10-month-old infant. D – NeuN-immunohistochemical staining, a region of the cortical plate within the calcarine sulcus, area 17, 10-month-old infant. E – mean NeuN-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 17. F – mean NeuN-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 18. Scale bar: 100 μm

Рис. 1. А – схема распределения NeuN-иммунореактивных клеток в коре затылочной доли у 10-месячного ребенка. В – диаграммы размаха и множественное сравнение коэффициента NeuN-иммунореактивности в кортикальной пластинке затылочной доли в трех областях: борозда, губа борозды и извилина, поля 17 (шпорная борозда) и 18 (теменно-затылочная борозда). Сравниваемые периоды: поздний фетальный период (LF), постнатальный период (PN), взрослые (А). Значимые различия между областями отмечены квадратными скобками. С – NeuN-иммуногистохимическое окрашивание, область кортикальной пластинки в губе шпорной борозды, поле 17, 10-месячный ребенок. D – NeuN-иммуногистохимическое окрашивание, область кортикальной пластинки внутри шпорной борозды, поле 17, 10-месячный ребенок. Е – график средних значений коэффициента NeuN-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 17. F – график средних значений коэффициента NeuN-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 18. Масштабная линейка: 100 мкм

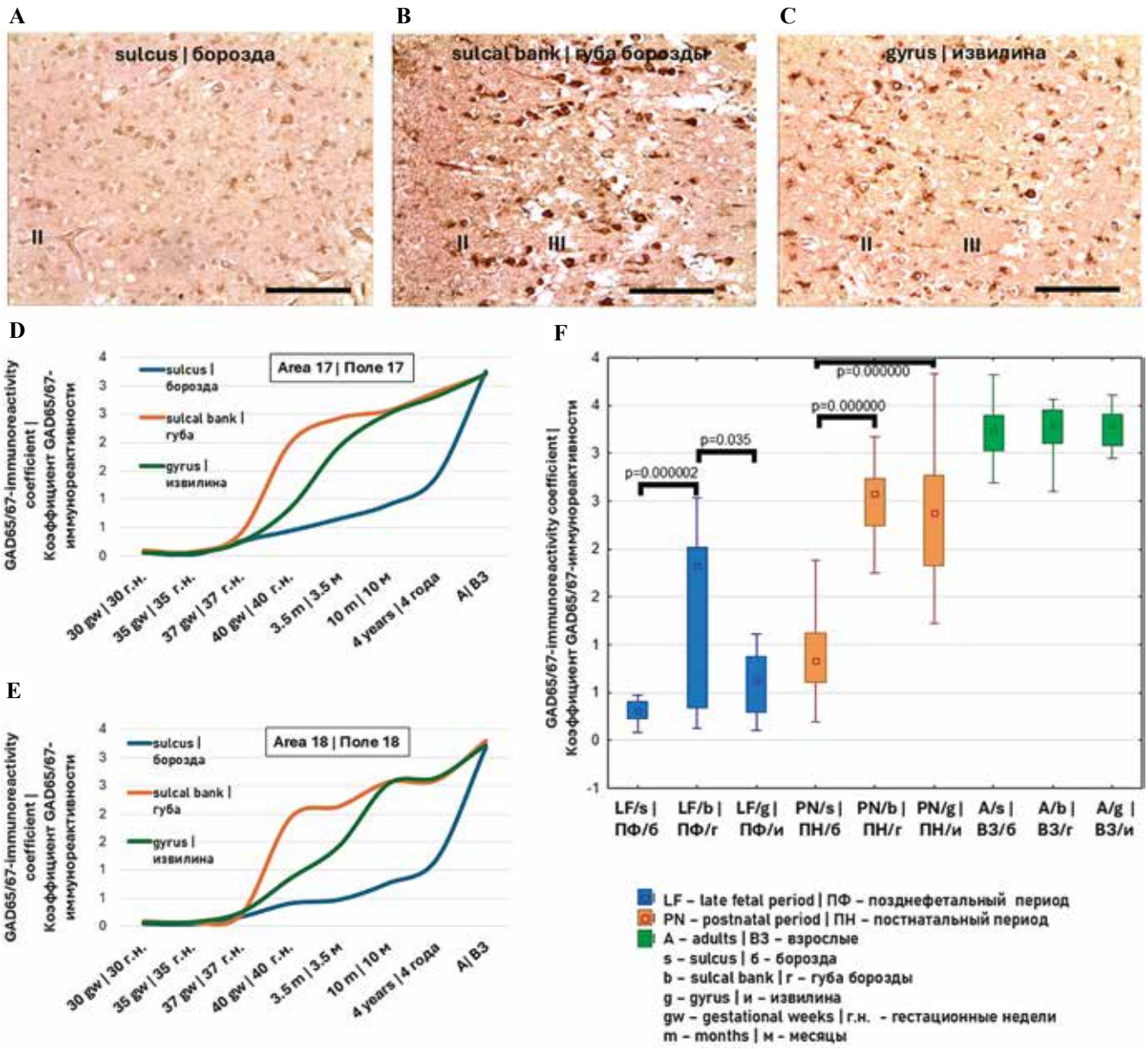

Fig. 2. GAD65/67 immunohistochemical staining of a coronal section of the human occipital lobe neocortex, 40 gestational weeks. A – a region of the cortical plate within the parieto-occipital sulcus, area 18. B – a region of the cortical plate at the bank of the parieto-occipital sulcus, area 18. C – a region of the cortical plate in the lingual gyrus, area 18. D – mean GAD65/67-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 17. E – graph of mean GAD65/67-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 18. F – boxplots and multiple comparisons for the GAD65/67-immunoreactivity coefficient in the cortical plate of the occipital lobe at three locations: sulcus, sulcal bank, and gyrus, areas 17 (calcarine sulcus) and 18 (parieto-occipital sulcus). Comparable periods: late fetal period (LF), postnatal period (PN), adults (A). Significant differences between locations are marked by brackets. Scale bar: 100 μm

Рис. 2. GAD65/67-иммуногистохимическое окрашивание коронарного среза неокортекса затылочной доли плода человека на 40-й неделе гестации (gw).
A – область кортикальной пластинки внутри теменно-затылочной борозды, поле 18. B – область кортикальной пластинки в губе теменно-затылочной борозды, поле 18. C – область кортикальной пластинки в язычной извилине, поле 18. D – график средних значений коэффициента GAD65/67-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 17. E – график средних значений коэффициента GAD65/67-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 18. F – диаграммы размаха и множественное сравнение коэффициента GAD65/67-иммунореактивности в кортикальной пластинке затылочной доли в трех областях: борозда, губа борозды и извилина, поля 17 (шпорная борозда) и 18 (теменно-затылочная борозда). Сравниваемые периоды: поздний фетальный период (LF), постнатальный период (PN), взрослые (A). Значимые различия между областями отмечены квадратными скобками. Масштабная линейка: 100 мкм

localizing in the marginal zone. A cytoarchitectonically specific pattern of immunopositive fiber arrangement in the marginal zone was noticeable. GAT-1 immunoreactivity of the cortex was the highest in the sulcal banks and gyri, with GAT-1 immunoreactivity decreasing when moving deeper into the sulci (Fig. 3 A, D). In area 17, the lower cortical layers and marginal zone showed prolonged immunohistochemical labeling, whereas in areas 18–19, the upper layers and marginal zone maintained stronger immunoreactivity over time. Postnatally, GAT-1 immunoreactivity in the sulcal bank cortex and the gyri cortex was comparable (Fig. 3 B, E). GAT-1 immunoreactivity in the sulcal cortex was significantly lower until 4 years postnatally (Fig. 4 A, B, C).

In adults, GAT-1-immunopositive fibers were primarily found in the cortex, with predominant labeling being in layer I. In adults, we observed no reduction in labeling within the sulci (Fig. 3 C, F).

GAT-1 immunoreactivity demonstrates that the gyri cortex and the sulcal bank cortex mature earlier than the cortex within the sulci. The delayed maturation of the sulci cortex persists until at least 4 years of age.

Discussion

Distribution of GAT-1, GAD65/67, and NeuN markers

Several studies have identified age-related changes in the levels of the synaptic activity markers GAT-1 [11] and GAD [12–14].

Our findings demonstrate predominant localization of the GAT-1 transporter to the marginal zone, consistent with earlier studies of the human neocortex [11]. However, due to the limited sample size, age-related changes could not be confirmed.

Literature reports significant changes in the GAD65 isoform expression but not in the GAD67 one [12]. Our study demonstrates the predominance of neuron body labeling, i.e., the GAD67 isoform labeling, in the late fetal period and newborns. According to the literature, this isoform appears earlier than others during human and animal ontogenesis [13, 14]. In the adult human cortex, immunolabeling revealed a predominance of fine, small fibers, i.e., GAD65 isoform, which is consistent with published data [13]. The quantity of the GAD67 isoform is likely to depend on the functional load of certain neu-

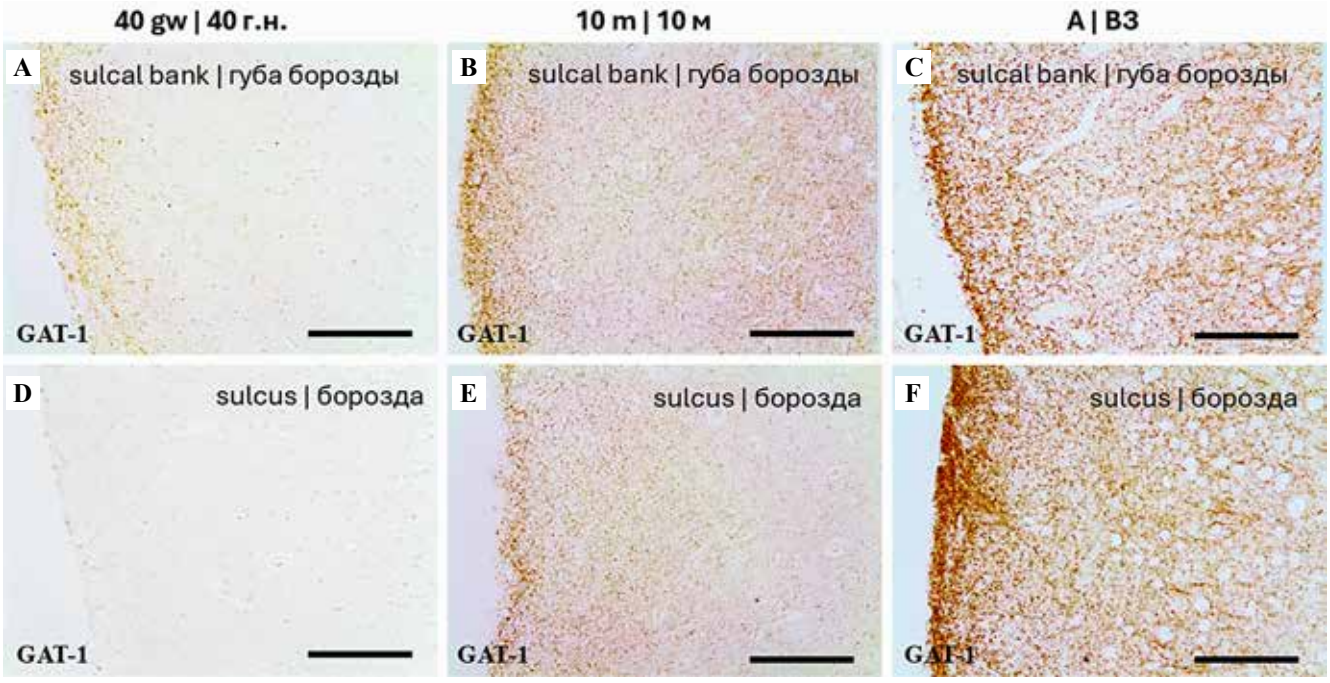

Fig. 3. GAT-1 immunohistochemical staining of a coronal section of the human occipital lobe.
A – a region of the marginal zone, cortical plate at the bank of parieto-occipital sulcus, area 18, 40 gestational weeks (gw). B – a region of the marginal zone, cortical plate at the bank of parieto-occipital sulcus, area 18, 10-month-old (m) infant. C – a region of the marginal zone, cortical plate at the bank of parieto-occipital sulcus, area 18, adult (A). D – a region of the marginal zone, cortical plate within the parieto-occipital sulcus, area 18, 40 gw. E – a region of the marginal zone, cortical plate within the parieto-occipital sulcus, area 18, 10-month-old infant. F – a region of the marginal zone, cortical plate within the parieto-occipital sulcus, area 18, adult. Scale bar: 100 μm

Рис. 3. GAT-1-иммуногистохимическое окрашивание коронарного среза затылочной доли человека.
A – область маргинальной зоны, кортикальная пластинка в губе теменно-затылочной борозды, поле 18, 40 недель гестации. B – область маргинальной зоны, кортикальная пластинка в губе теменно-затылочной борозды, поле 18, 10-месячный (м) ребенок. C – область маргинальной зоны, кортикальная пластинка в губе теменно-затылочной борозды, поле 18, взрослый (B3). D – область маргинальной зоны, кортикальная пластинка внутри теменно-затылочной борозды, поле 18, 40 недель гестации. E – область маргинальной зоны, кортикальная пластинка внутри теменно-затылочной борозды, поле 18, 10-месячный ребенок. F – область маргинальной зоны, кортикальная пластинка внутри теменно-затылочной борозды, поле 18, взрослый. Масштабная линейка: 100 мкм

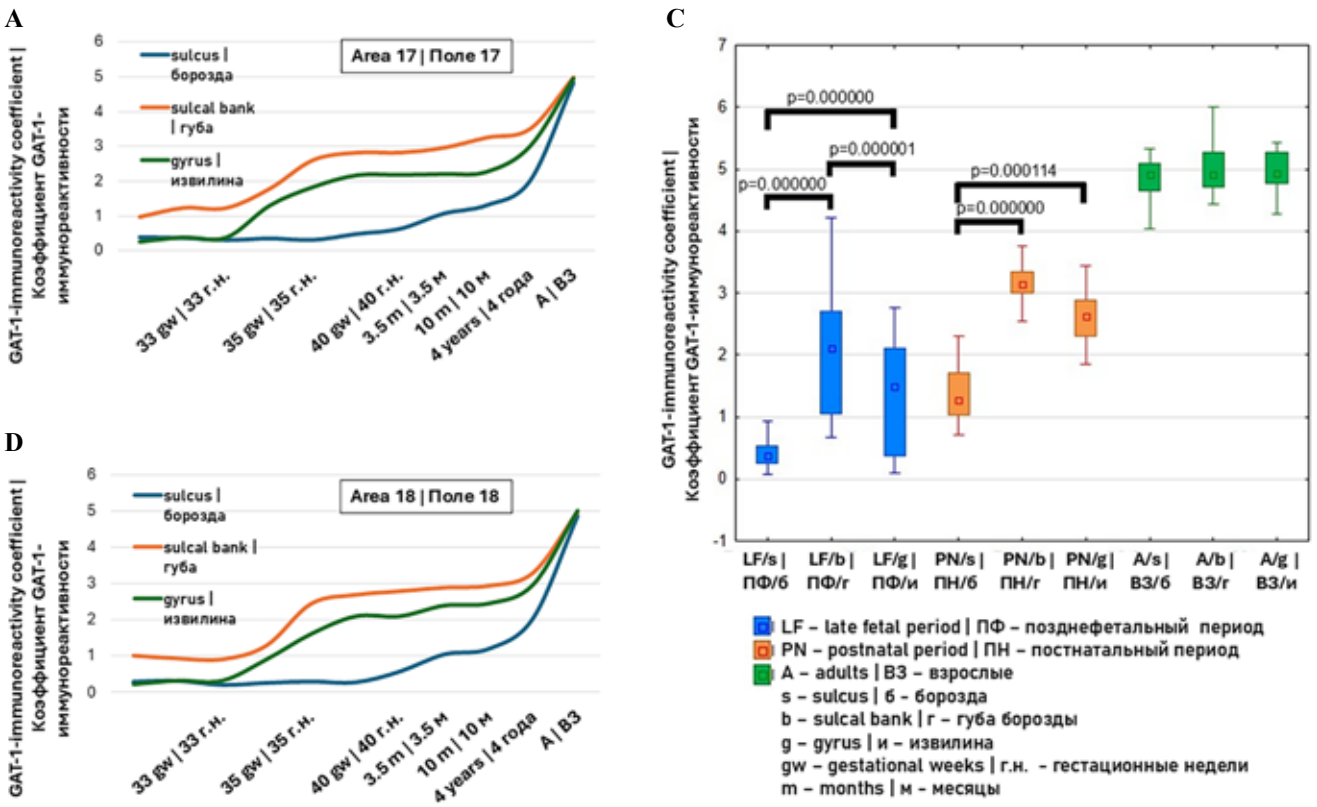

Fig. 4. A – mean GAT-1-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 17. B – mean GAT-1-immunoreactivity coefficient in the cortical plate of the sulcus, sulcal bank, and gyrus as a function of age, area 18. C – boxplots and multiple comparison for the GAT-1-immunoreactivity coefficient in the cortical plate of the occipital lobe at three locations: sulcus, sulcal bank, and gyrus, areas 17 (calcarine sulcus) and 18 (parieto-occipital sulcus). Comparable periods: late fetal period (LF), postnatal period (PN), adults (A). Significant differences between locations are marked by brackets

Рис. 4. А – график средних значений GAT-1-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 17. В – график средних значений GAT-1-иммунореактивности в кортикальной пластинке борозды, губы борозды и извилины в зависимости от возраста, поле 18. С – диаграммы размаха и множественное сравнение коэффициента GAT-1-иммунореактивности в кортикальной пластинке затылочной доли в трех областях: борозда, губа борозды и извилина, поля 17 (шпорная борозда) и 18 (теменно-затылочная борозда). Сравниваемые периоды: поздний фетальный период (LF), постнатальный период (PN), взрослые (А). Значимые различия между областями отмечены квадратными скобками

rons. A similar dependence was confirmed for the GAD65 isoform [15].

This paper reveals differing immunoreactivity to GAT-1, GAD65/67, and NeuN in sulci, sulcal banks, and gyri. We showed higher immunoreactivity coefficient values in sulcal banks and gyri in the late fetal period, which continued in the postnatal period until 4 years postnatally. In the adult samples, we observed no heterogeneity in the distribution of the markers in the cortex of sulci and gyri.

Neocortical neurons from vertical columnar assemblies span all cortical layers. Neurons within a column process signals of a single modality [16], a functional architecture established in early cortical development. Each column contains cells derived from multiple clones of a common origin [17]. In the adult brain, these columns group into larger second-order assemblies—macrocolumns—which typically consist of 3–12 columns [18].

Previous studies visualized macrocolumns with GAD67 immunohistochemistry in both the developing and mature rat brain [19]. In cats, transient visualization of second-order morphological and functional structures was observed with the labeling of excitatory receptors NMDAR1 during normal brain development [20].

Our findings reveal second-order morphological and functional assemblies in the human neonatal cortex using GAD labeling. In newborns, GAD-immunopositive neuron bodies were found in area 17.

Additionally, NeuN labeling has temporarily revealed morphological and functional assemblies in a 10-month-old infant, localized within the sulci of the neocortex. *In vivo* imaging in mice demonstrated that prospective interneurons form patches of correlated activity that merge during postnatal development. This functional organization changes rapidly in two steps: by the end of the postnatal week, GABA assemblies form; two days later, these assemblies merge into a fully connected functional network [21]. As a result, the clustered functional organization of the cortex is a transient developmental stage in mice. The persistence

of morphological features of the clustered organization within the sulci in the human neocortex at 10 months may indirectly indicate a slower maturation rate in these regions.

Thus, immunohistochemical labeling of GAD65/67 and NeuN shows that cortical maturation progresses in clusters, representing second-order functional neural assemblies. Comparative analysis using GAT-1, GAD65/67, and NeuN markers indicates a more accelerated cortical maturation in the sulcal banks and gyri than in the cortex within the sulci.

Conclusion

This research studied the complex maturation of the human cerebral cortex within sulci and gyri during late fetal and postnatal development, thus addressing a significant gap in our understanding of neocortical formation. Cortical maturation progresses heterogeneously and is characterized by the formation of second-order functional neural assemblies, as visualized using GAD65/67 and NeuN markers. Specifically, cortical regions of sulcal banks and gyri mature earlier than the sulci, as confirmed by the distribution patterns of GAT-1, GAD65/67, and NeuN. These data indicate a differentiated maturation pattern in the gyrified cortex, where regions at the boundaries of sulci and gyri were shown to mature earlier than sulcal regions.

The paper highlights the complex interplay between gyrification and cortical maturation, suggesting a strong link between the cortical structural organization and its functional development. Future research should elucidate the mechanisms underlying heterogeneity in cortical maturation and investigate their functional consequences. These studies could provide a more comprehensive understanding of normal brain development and help uncover diagnostic and therapeutic targets for neurodevelopmental disorders.

Author contributions

Conceived the study and designed the experiment – O.S. Godovalova, A.E. Proshchina, S.V. Saveliev.
Collected the data and performed the analysis – A.S. Kharlamova, O.S. Godovalova.
Wrote the paper – O.S. Godovalova.
Edited the manuscript – Yu.S. Krivova, A.E. Proshchina, A.S. Kharlamova.

Вклад авторов

Концепция и дизайн исследования – О.С. Годовалова, А.Е. Прощина, С.В. Савельев.
Сбор и обработка материала – А.С. Харламова, О.С. Годовалова.
Написание текста – О.С. Годовалова.
Редактирование – Ю.С. Кривова, А.Е. Прощина, А.И. Харламова.

Disclosure. The authors declare no conflict of interest.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

References/Литература

1. *Godovalova O, Proshchina A, Kharlamova A, Barabanov V, Krivova Y, Junemann O et al.* Heterogeneity in the formation of primary and secondary visual fields during human prenatal development. Biol Res. 2024;57(1):93. DOI: 10.1186/s40659-024-00576-0.
2. *Huttenlocher PR, Dabholkar AS.* Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997;387(2):167–78. DOI: 10.1002/(sici)1096-9861(19971020)387:2<167::aid-cne1>3.0.co;2-z.
3. *Kim JY, Paredes MF.* Implications of extended inhibitory neuron development. Int J Mol Sci. 2021;22(10):5113. DOI: 10.3390/ijms22105113.
4. *Amunts K, Malikovic A, Mohlberg H, Schormann T, Zilles K.* Brodmann's areas 17 and 18 brought into stereotaxic space – where and how variable? Neuroimage. 2000;11(1):66–84. DOI: 10.1006/nimg.1999.0516.
5. *Lee SE, Lee Y, Lee GH.* The regulation of glutamic acid decarboxylases in GABA neurotransmission in the brain. Arch Pharm Res. 2019;42(12):1031–9. DOI: 10.1007/s12272-019-01196-z.
6. *Fattorini G, Melone M, Conti F.* A reappraisal of GAT-1 localization in neocortex. Front Cell Neurosci. 2020;14:9. DOI: 10.3389/fncel.2020.00009.
7. *Duan W, Zhang YP, Hou Z, Huang C, Zhu H, Zhang CQ at al.* Novel insights into NeuN: from neuronal marker to splicing regulator. Mol Neurobiol. 2016;53(3):1637–47. DOI: 10.1007/s12035-015-9122-5.
8. *Gilbert-Barness E, Spicer DE, Steffensen TS.* Handbook of pediatric autopsy pathology. New York: Springer New York, 2014. 750 p. DOI: 10.1007/978-1-4614-6711-3.
9. *Proshchina A, Kharlamova A, Krivova Y, Godovalova O, Otlyga D, Gulimova V et al.* Neuromorphological atlas of human prenatal brain development: white paper. Life (Basel). 2023;13(5):1182. DOI: 10.3390/life13051182.
10. *Proshchina AE, Kharlamova AS, Krivova YS, Saveliev SV.* Modern trends in brain mapping and atlasing. Clinical and experimental morphology. 2023;12(1):15–23 (In Russ.). DOI: 10.31088/CEM2023.12.1.15-23.
11. *Hachiya Y, Takashima S.* Development of GABAergic neurons and their transporter in human temporal cortex. Pediatr Neurol. 2001;25(5):390–6. DOI: 10.1016/s0887-8994(01)00348-4.
12. *Pinto JG, Hornby KR, Jones DG, Murphy KM.* Developmental changes in GABAergic mechanisms in human visual cortex across the lifespan. Front Cell Neurosci. 2010;4:16. DOI: 10.3389/fncel.2010.00016.
13. *Murphy KM, Beston BR, Boley PM, Jones DG.* Development of human visual cortex: a balance between excitatory and inhibitory plasticity mechanisms. Dev Psychobiol. 2005;46(3):209–21. DOI: 10.1002/dev.20053.
14. *Wong PT, McGeer EG.* Postnatal changes of GABAergic and glutamatergic parameters. Dev Brain Res. 1981;227(4):519–29. DOI: 10.1016/0165-3806(81)90005-5.
15. *Soghomonian JJ, Martin DL.* Two isoforms of glutamate decarboxylase: why? Trends Pharmacol Sci. 1998;19(12):500–5. DOI: 10.1016/s0165-6147(98)01270-x.
16. *Molnár Z, Clowry GJ, Šestan N, Alzu'bi A, Bakken T, Hevner RF et al.* New insights into the development of the human cerebral cortex. J Anat. 2019;235(3):432–51. DOI: 10.1111/joa.13055.
17. *Yuste R, Cossart R, Yaksi E.* Neuronal ensembles: building blocks of neural circuits. Neuron. 2024;112(6):875–92. DOI: 10.1016/j.neuron.2023.12.008.

18. *Rakic P.* A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci. 1995;18(9):383–8. DOI: 10.1016/0166-2236(95)93934-p.
19. *Kiser PJ, Cooper NG, Mower GD.* Expression of two forms of glutamic acid decarboxylase (GAD67 and GAD65) during postnatal development of rat somatosensory barrel cortex. J Comp Neurol. 1998;7;402(1):62–74. PMID: 9831046.
20. *Trepel C, Duffy KR, Pegado VD, Murphy KM.* Patchy distribution of NMDAR1 subunit immunoreactivity in developing visual cortex. J Neurosci. 1998;18(9):3404–15. DOI: 10.1523/JNEUROSCI.18-09-03404.1998.
21. *Modol L, Bollmann Y, Tressard T, Baude A, Che A, Duan ZRS et al.* Assemblies of perisomatic GABAergic neurons in the developing barrel cortex. Neuron. 2020;105(1):93–105.e4. DOI: 10.1016/j.neuron.2019.10.007.

Author information

Olga S. Godovalova – Cand. Sci. (Biol.), Senior Researcher, Laboratory of Nervous System Development, Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Centre of Surgery”.
https://orcid.org/0000-0002-9285-7241

Alexandra E. Proshchina – Dr. Sci. (Biol.), Leading Researcher, Laboratory of Nervous System Development, Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Centre of Surgery”.
https://orcid.org/0000-0002-0515-8275

Anastasia S. Kharlamova – Cand. Sci. (Biol.), Senior Researcher, Laboratory of Nervous System Development, Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Centre of Surgery”.
https://orcid.org/0000-0003-1163-4132

Yuliya S. Krivova – Cand. Sci. (Biol.), Senior Researcher, Laboratory of Nervous System Development, Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Centre of Surgery”.
https://orcid.org/0000-0001-9692-3616

Sergey S. Saveliev – Dr. Sci. (Biol.), Professor, Head of Laboratory of Nervous System Development, Avtsyn Research Institute of Human Morphology of FSBSI “Petrovsky National Research Centre of Surgery”.
https://orcid.org/0000-0002-1447-7198

Информация об авторах

Ольга Сергеевна Годовалова – кандидат биологических наук, старший научный сотрудник лаборатории развития нервной системы НИИ морфологии человека им. акад. А.П. Авцына РНЦХ им. акад. Б.В. Петровского.

Александра Евгеньевна Прощина – доктор биологических наук, ведущий научный сотрудник лаборатории развития нервной системы НИИ морфологии человека им. акад. А.П. Авцына РНЦХ им. акад. Б.В. Петровского.

Анастасия Сергеевна Харламова – кандидат биологических наук, старший научный сотрудник лаборатории развития нервной системы НИИ морфологии человека им. акад. А.П. Авцына РНЦХ им. акад. Б.В. Петровского.

Юлия Сергеевна Кривова – кандидат биологических наук, старший научный сотрудник лаборатории развития нервной системы НИИ морфологии человека им. акад. А.П. Авцына РНЦХ им. акад. Б.В. Петровского.

Сергей Вячеславович Савельев – доктор биологических наук, профессор, заведующий лабораторией развития нервной системы НИИ морфологии человека им. акад. А.П. Авцына РНЦХ им. акад. Б.В. Петровского.