UDC 61

FEATURES OF THE AGE DEVELOPMENT OF THE PREFRONTAL CORTEX

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Annotation. The widespread belief that the maturation of the prefrontal cortex is complete by the age of 25, which may explain the behavioral immaturity of some adolescents, simplifies the complex process of neurodevelopment. However, MRI studies and neurobiological data indicate that neuronal differentiation, synaptic remodeling, and myelination continue until the age of 30 and beyond. This emphasizes the need to revise the established ideas about the “critical age” of brain maturation. The purpose of this work was a literature review of researches devoted to the study of age-related brain development, in particular the prefrontal cortex.

Keywords: Prefrontal cortex, adolescents, age development, mediator, synapse.

The main part. The prefrontal cortex is a brain regions with a largely heterogeneous cross-species anatomical structure that is responsible for numerous cognitive abilities. In humans, the prefrontal cortex occupies about 30% of the brain surface [1]. Its development is longer than that of the sensory cortex and is controlled by molecular signals that determine the proliferation, migration, differentiation, and final boundaries of prefrontal neurons [2].

By the age of five years, the brain has increased in weight from 26% to about 88% of its adult weight. This number is often used to support the popular claim that the brain is 90% developed by the age of five [3]. However, another study has shown the growth of the human brain over the course of a lifetime, examining the volumes of different brain tissues using 123,984 MRI scans of 101,457 participants. The age

range of the participants was very wide, from 115 days after conception to 100 years. It has been shown that the morphology of the brain undergoes a long and complex process of maturation from pregnancy to the third decade of life, calling into question the previously stated clear cut limit of 25 years [4]. Furthermore, brain weight does not always correspond to its maturity. Much more important is to understand the fundamental principles of brain function, which are formed in the early stages of development and affect its activity throughout life [3].

The typical maturation of the cerebral cortex is characterized by a hierarchical thinning of the cortex from the primary cortex to the association cortex [5], and is mediated by cellular mechanisms, genetic regulation, and biomechanical factors [6]. After neuronal proliferation and the formation of an excess of synaptic connections, the brain is reprogrammed during the period from the onset of puberty to 24 years, especially in the prefrontal cortex, by dendritic pruning of unused synapses and myelination, which increases the speed of information processing. Thus, in the mature brain, up to 60% of the synapses at the beginning of life will be preserved [7].

Fetal programming shows that in the beginning the brain incorporates experience into its architecture, but at the same time the process of synaptic pruning is regulated by experience: neural connections that are regularly activated undergo strengthening and stabilization, while synapses with low activity undergo degradation and disappear. The activity of neural networks stimulates their functional strengthening, ensuring the optimization of the synaptic organization of the brain [4].

Separately, age-related features of the development of neurotransmitter systems should be highlighted. Thus, dopamine in limbic areas is considered to be the main substrate of motivational behavior. The administration of dopamine or dopamine agonists into these areas initiates novelty-seeking and goal-directed behavior, whereas the administration of dopamine antagonists has the opposite effect. In addition, adult rats that exhibit higher levels of motor activity and novelty-seeking exhibit higher levels of drug self-administration and increased dopamine concentrations compared with rats that exhibit low baseline activity [8].

The significant reorganization of the dopamine system during adolescence

partly underlies the associated behavioral changes and increased vulnerability [9]. The selective α6 (α6-nicotinic acetylcholine receptor) blocker, α-conotoxin, increased dopamine release in rats in early adolescence but decreased dopamine release in rats from mid-adolescence through adulthood.

A study using MRI and PET found that D_2/D_3 receptor availability decreases with age, while presynaptic dopamine stores stabilize after approximately 18 years of age, indicating functional specialization and completion of dopamine system maturation during the transition from adolescence to adulthood [10].

By day 36 after birth, activation of dopamine D1 receptors in GABAergic interneurons enhances their activity, while stimulation of D2 receptors has little or no inhibitory effect. After adolescence, the situation changes: activation of D2 receptors begins to have an excitatory effect on these interneurons, which ensures the formation of a stable inhibitory tone characteristic of the mature prefrontal cortex. This helps to balance the increased excitation of pyramidal neurons caused by dopamine.

The frontolimbic network is driven by glutamatergic and dopaminergic signaling and determines motivated behavior and personality traits. In adolescents, reward-seeking behavior changes with the maturation of the prefrontal cortex, striatum, and amygdala [11].

During adolescence, changes occur in the architecture and function of excitatory and inhibitory neurons and synapses, which together lead to a recalibration of the excitation/inhibition ratio. Postmortem studies of the adolescent prefrontal cortex have shown a reduction in the density of excitatory (glutamatergic) synapses. Transcriptomic analyses have revealed marked changes in the expression of genes associated with inhibitory neurons (parvalbumin-positive interneuron subunits and GABA-A receptors), reflecting the maturation of inhibitory function and manifested by an increase in the amplitude and a reduction in the duration of inhibitory postsynaptic currents, which generally indicates an increase in the efficiency and accuracy of inhibitory synaptic transmission in the prefrontal cortex. [12].

Thinning of the cerebral cortex is an important feature of the maturation of brain morphology during childhood and adolescence. From a multifaceted

developmental perspective, anatomical improvements in neuronal layers at local gyri and sulci, such as synaptic pruning and myelination, and tension exerted by white matter fibers may collectively contribute to cortical maturation [13].

A study of the impact of lockdowns imposed during the COVID-19 pandemic found that enforced social isolation had a negative impact on the development and maturation of the CNS in adolescents. Using MRI data from before and after the pandemic, researchers found accelerated thinning of the cerebral cortex, which was more pronounced in girls compared to boys. On average, the rate of this acceleration corresponded to approximately 4.2 years of additional development in girls and 1.4 years in boys [14].

In addition, numerous previous studies of adverse conditions in children and adolescents have shown that adverse conditions lead to similar premature brain maturation [15]. For example, a study involving children aged 9 to 13 years showed accelerated maturation of the medial prefrontal cortex, responsible for higher cognitive processes, which was reflected in a decrease in cortical thickness (i.e., synaptic pruning - the process of eliminating or weakening synapses [16]) compared to what is expected with normal aging, and accelerated development of the hippocampus, which was reflected in an increase in its volume [17]. This suggests that chronic stress and environmental factors can significantly alter the rate of brain maturation during adolescence, supporting the idea that the development of prefrontal areas and associative networks is long-term and sensitive to external influences, with the process of full maturity occurring in late adolescence [14].

Conclusion. Prefrontal cortex neurons are formed before birth, and their differentiation, synapse development, and functional specialization continue until the age of 25–30. During this period, excessive synapse formation occurs with subsequent selective elimination, and myelination and reorganization of neural networks ensure the gradual maturation of cognitive and emotional functions. Despite the generally accepted estimate of the completion of brain maturation at about 25 years of age, MRI data indicate a long and variable development that depends on individual and external factors.

REFERENCES

1. Carlen M. What constitutes the prefrontal cortex? Science. 2017;358:478–82. https://doi.org/10.1126/science.aan8868.

2. Chini M., Hanganu-Opatz I.L. Prefrontal Cortex Development in Health and Disease: Lessons from Rodents and Humans Trends in Neurosciences. 2020; 44(3): 227 – 240. https://doi.org/10.1016/j.tins.2020.10.017

3. Thompson R. A. (2024). Early Brain Development and Public Health. Delaware journal of public health, 10(4), 6–11. https://doi.org/10.32481/djph.2024.10.03

4. Bethlehem, R.A.I., Seidlitz, J., White, S.R. et al. Brain charts for the human lifespan. Nature. 2022; 604: 525–533. https://doi.org/10.1038/s41586-022-04554-y

5. Frangou S, Modabbernia A, Williams SCR, et al. Cortical thickness across the lifespan: Data from 17,075 healthy individuals aged 3-90 years. Hum Brain Mapp. 2022;43(1):431-451. doi:10.1002/hbm.25364

6. van Drunen L, Toenders YJ, Wierenga LM, Crone EA. Effects of COVID-19 pandemic on structural brain development in early adolescence. Sci Rep. 2023;13(1):5600. doi:10.1038/s41598-023-32754-7

7. Center for the Developing Child. (2024). Brain architecture. Retrieved July 8, 2024 from https://developingchild.harvard.edu/science/key-concepts/brain-architecture/

8. Wahlstrom, D., Collins, P., White, T., & Luciana, M. (2010). Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. Brain and cognition, 72(1), 146–159. https://doi.org/10.1016/j.bandc.2009.10.013

9. Iacino MC, Stowe TA, Pitts EG, Sexton LL, Macauley SL, Ferris MJ. A unique multi-synaptic mechanism involving acetylcholine and GABA regulates dopamine release in the nucleus accumbens through early adolescence in male rats. Elife. 2024;13:e62999. doi:10.7554/eLife.62999

10. Larsen, B., Olafsson, V., Calabro, F., Laymon, C., Tervo-Clemmens, B., Campbell, E., Minhas, D., Montez, D., Price, J., & Luna, B. (2020). Maturation of the human striatal dopamine system revealed by PET and quantitative MRI. Nature

communications, 11(1), 846. https://doi.org/10.1038/s41467-020-14693-3

11. Gleich, T., Lorenz, R. C., Pöhland, L., Raufelder, D., Deserno, L., Beck, A., Heinz, A., Kühn, S., & Gallinat, J. (2015). Frontal glutamate and reward processing in adolescence and adulthood. Brain structure & function, 220(6), 3087–3099. https://doi.org/10.1007/s00429-014-0844-3

12. Amanda E. Baker, Adriana Galván, Andrew J. Fuligni. The connecting brain in context: How adolescent plasticity supports learning and development. Developmental Cognitive Neuroscience. 2025; 71:101486. https://doi.org/10.1016/j.dcn.2024.101486.

13. Norbom, L. B. et al. New insights into the dynamic development of the cerebral cortex in childhood and adolescence: Integrating macro-and microstructural MRI findings. Progress in Neurobiology. 2021;204:102109. https://doi.org/10.1016/j.pneurobio.2021.102109.

14. Corrigan NM, Rokem A, Kuhl PK. COVID-19 lockdown effects on adolescent brain structure suggest accelerated maturation that is more pronounced in females than in males. Proc Natl Acad Sci U S A. 2024 Sep 17;121(38):e2403200121. doi: 10.1073/pnas.2403200121.

15. Colich, N. L., Rosen, M. L., Williams, E. S., & McLaughlin, K. A. (2020). Biological aging in childhood and adolescence following experiences of threat and deprivation: A systematic review and meta-analysis. Psychological bulletin, 146(9), 721–764. https://doi.org/10.1037/bul0000270

16. Faust, Travis E.; Gunner, Georgia; Schafer, Dorothy P. (November 2021). "Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS". Nature Reviews. Neuroscience. 22 (11): 657–673. doi:10.1038/s41583-021-00507-y.

17. van Drunen, L., Toenders, Y.J., Wierenga, L.M. et al. Effects of COVID-19 pandemic on structural brain development in early adolescence. Sci Rep 13, 5600 (2023). https://doi.org/10.1038/s41598-023-32754-7