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REVIEW ARTICLE

THE ADOLESCENT BRAIN - CHANGES AND CHALLENGES OF DEVELOPMENT

ADOLESCENTNI MOZAK – PROMENE I IZAZOVI RAZVOJA

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ABSTRACT

Adolescence is a period between childhood and adulthood, characterized by specific physical and psychological development. It is a transitional developmental period, rather than a single snapshot in time. Traditional neurobiological and cognitive explanations of adolescent development of behavior have failed to account for the changes in behavior observed during adolescence. Magnetic resonance imaging studies have discovered that myelinogenesis continues from childhood to adulthood in the brain's region-specific neurocircuitry, which remains structurally and functionally vulnerable to impulsive habits. The maturation of the adolescent brain is influenced by heredity, environment, and sex, and they play a crucial role in myelination. Furthermore, one of the measures extracted out of MRI studies is also the thickness of cerebral cortex, a part that harbors synapses. It is the complexity of these synapses that allows humans to generate and understand complex thoughts and feelings in the real world, including the ability to solve analogies. And it is the complexity of those connections, remaining under construction during adolescence, that may be responsible for immature and impulsive behavior and neurobehavioral excitement during the adolescent life.

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SAŽETAK

Adolescencija je period fizičkog i psihološkog razvoja, koji se odvija između detinjstva i perioda odraslog života. To je više prelazni razvojni period nego što je izolovan trenutak u vremenu. Tradicionalna neurobiološka i kognitivna objašnjenja razvoja adolescenta nisu uspela da obrazlože promene u ponašanju koje se primećuju tokom adolescencije. Naučne studije su otkrile da se mijelogeneza nastavlja u specifičnim neuronskim mrežama mozga od detinjstva do zrelosti. Sazrevanje adolescentnog mozga je pod uticajem nasleđa, okruženja i pola, koji igraju presudnu ulogu u mijelinizaciji. Složenost razvoja sinapsi omogućava ljudima stvaranje i razumevanje kompleksnih misli i osećanja, uključujući i sposobnost rešavanja analogija u realnom svetu. I sama kompleksnost ovih veza, koje nastavljaju razvoj tokom adolescencije, može da bude odgovorna kako za nezrelo i impulsivno ponašanje, tako i za neurobihejvioralno uzbuđenje tokom adolescentnog života

Ključne reči:
dijagnoza,
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psihijatrija

Introduction

Throughout the history, adolescents were thought to be influenced by dark forces. As Aristotle stated more than 2300 years ago, "the young are heated by nature as drunken man by wine". In the William Shakespeare Winter's Tale, shepherd whishes "there were no age between ten and thee-and-twenty, or that youth would sleep out the rest: for there is nothing in the between but getting wenches with child, wronging ancientry, stealing, fighting". Stanly Hall, one of the first contemporary scientists in the field of adolescence, the author of the book Adolescence: Its psychology and its relation to physiology and anthropology, sociology, sex, crime, religion and education, believed that this period, a period of "storm and stress", mirrored earlier stages of human development (1). Freud perceived adolescence as an expression of torturous psychosexual conflict. Erickson saw adolescence as the most important period of psychosocial development, and explained several stages of crisis throughout this particular phase of life (2).

Following infancy, adolescence is one of the most dynamic events of human growth and development, in terms of the amount of change in the brain. The brain undergoes the process of "rewiring" that is not completed until around the age of 25 (3). The rewiring is achieved by dendritic pruning and myelination. Dendritic pruning disposes the unused synapses, whereas myelination increases the speed of impulse conduction across the neurocircuitries. Both processes are very important for accomplishing efficient neurocybernetics in the adolescent brain (3, 4). Adolescents experience numerous coinciding changes in the somatic, social and academic spheres, and are prone to various environmental influences as they enter a stage of profound psychological transition. Molecular imaging and functional genomics studies have indicated that the brain remains in an active development during adolescence (5). In particular, magnetic resonance imaging (MRI) studies have discovered that myelinogenesis continues and that the neurocircuitries are affected by peripubertal surges of sex hormones, influencing sex, eating, and sleeping habits, along with the involvement of environmental cues (3). Particularly significant changes occur in the limbic system, associated with self-control, decision making, emotions, and risk-taking behaviors (5, 6). Sex hormones, that specifically surge during puberty, are involved in transcriptional regulation of the neurocircuitry and myelinogenesis (3, 7).

Normal development of the adolescent brain is aimed at balancing impulses, desires, goals, self-interests, rules, ethics and even altruism, to generate a more complex, and ultimately, a more mature behavior. However, this complex behavior may take another path, characterized by doing actions that lead to a higher chance of adverse outcomes such as accidental injuries, violence, substance abuse and unplanned pregnancy (6).

The adolescent maturation of the brain is dependent on both hereditary (genetic) and environmental factors (such as prenatal and postnatal insults, nutritional status, sleep patterns, pharmacotherapy, surgical interventions during early childhood) (7). It may also be affected by physical, mental, economical and psychological stress, drug abuse, as well as sex hormones including estrogen, progesterone, and other (8).

Pre-Puberty and Neurodevelopment

Jay N. Giedd was the first to analyze the serial scans of adolescents brain, assessing over 100 people as they grew up during the nineties, noticing the massive brain reorganization between the ages of 12 and 25 (4, 6). The brain doesn't grow very much in size during this period, as it reaches 90% of its full size by the age of 6, and further scull thickening limits the additional brain growth (4-7). However, what happens in adolescence is the remodeling of the brain, with the upgrade of networks and wiring.

Brain develops through two processes. The first one refers to the overproduction of neural cells and synapses, and is determined by genes and environment (available nutrition, stimulation, toxins, infections, injuries). This is followed by the second process - the competitive elimination of cells and synapses, selecting those that are more important for person's activities and needs (as well, determined by hereditary factors, environment and physiology). The most intensive overproduction happens during the first 18 months of life. The second wave of overproduction is located mostly in the prefrontal area of the

brain cortex, a region that controls judgment, control, organization, planning. That second period occurs during pre-puberty, and it peaks around age of 11 in girls, 12 in boys, roughly around the onset of puberty. This results in further thickening of grey mater (7, 9, 10).

Puberty and Neurodevelopment

The adolescence begins with the onset of puberty, and is therefore driven by changes in hormone levels and physical appearance. The data on the relationship between puberty and neurodevelopment in humans is scarce, but the results of animal studies imply that hormonal events of puberty influence the brain maturation and behavior (6, 11).

It is believed that neurodevelopmental consequences of gonadal hormones are occurring via two relatively distinctive processes - organization and activation (10, 12). Organizational effects occur pre-and perinatally, as testosterone waves masculinize and defeminize neurocircuits in males, with the absence of testosterone resulting in a female neuro-phenotype. The activation effect occurs in puberty as hormones affect the dormant neural circuits. These events are also involved in organizing the neurocircuitry of adult social and reproductive behavior (13).
The changes of cortical grey matter in density, volume and thickness during childhood and adolescence, happen in a region-specific and predominately nonlinear manner. The time when grey matter volume peaks, corresponds to the sexually dimorphic ages of gonadarche onset, suggesting possible interaction between puberty hormones and grey matter development (14).

The peak of the second wave of overproduction is followed by the intensive selection of cells and synapses during adolescence, through process of "pruning", when excess connections are being eliminated. The cerebral cortex gets thinner between the ages of 14 and 24, with the greatest amount of change in the association cortex (the regions used for complex thought and reasoning) (15). Indeed, we are born with more neurons than we'll ever have during our life, and one of the most important developmental processes - the synaptic refinement, known as "pruning", eliminates some of the connections to ensure our brain is working more efficiently (15).

As mentioned earlier, most of the brain change during adolescence takes place in the association cortex, which is probably related to the prolonged development of these regions. The other regions of the brain are more similar to their adult structure and their development is slowing down by the age of 14. Considering the importance of synapses being pruned away, it makes sense to keep as many synapses as needed for a longer time, until it is known which connections will be most efficient for optimal reasoning in the complex world around us (15). Using MRI to measure cortical thickness and intracortical myelination in 14–24 year old volunteers, it was found and replicated that associative cortical areas were thicker and less myelinated than primary cortical areas at the age of 14; however, the associative cortex had faster rates of shrinkage and myelination over the course of adolescence (15). Adolescent cortical myelination and shrinkage were coupled, and specifically associated with the enriched expression of the synaptic, oligodendroglial and schizophrenia-related genes (15). Topologically efficient and biologically "expensive" hubs of the brain anatomical network, had greater rates of shrinkage and myelination, and were associated with overexpression of the same transcriptional profile as cortical consolidation. Developmental variation of this consolidation process may be relevant both to normal cognitive and behavioral changes, and the high incidence of schizophrenia – a psychiatric disorder that is most likely to emerge during human late teenage years i.e. the late adolescence (15).

Neurobiological Model of Adolescence

In the past, the adolescence has been associated with controversies and myths. The traditional neurobiological and cognitive explanation of adolescent behavior failed to clarify the nonlinear changes observed during adolescence, relative to both childhood and adulthood (6). There were numerous reports that linked adolescent behavior to protracted development of prefrontal cortex. If this was the case, then children would show similar or even more complicated behavior than adolescents. Adolescents do engage in more activities that can put them in more risky situations (driving a car, consuming alcohol), but this still is not enough to explain the nonlinear elevation in risky behaviors in adolescents comparing to children (11). Furthermore, not only that some experimental studies have shown that children perceive greater risk in hypothetical situations, than adolescents do (6), but this has also been mirrored by mortality rates that were more than tripled in those aged from 15 - 24, comparing to those aged from 11 - 14 (3). It has been suggested by Casey et al (6), based on human imaging studies, that there is a rise in subcortical activation (n. accumbens and amygdale) among adolescents when making risky choices or processing emotional information, relative to children and adults; similar assumptions were given after analyzing numerous animal studies (10). Unlike tubulinogenesis, axonogenesis and synaptogenesis (that are accomplished during prenatal and immediate postnatal life), the myelinogenesis remains active during the adolescent life. The glutamatergic neurotransmission is also accomplished during prenatal and early postnatal life, whereas the GABAergic transmission remains under construction throughout the adolescence (16). Animal studies point out the overproduction of axons and synapses in limbic system and prefrontal cortex during pre-puberty, followed by rapid pruning in adolescence (17). Like in humans, there is also a continual growth in the density of the fibers connecting the amygdale and prefrontal cortex into early adulthood (18). Animal studies have also confirmed that the

prefrontal cortex matures later than nucleus accumbens (19, 20) and that dopamine levels and projections are crucial for the communication between prefrontal cortex and limbic system (6). Signaling between them relies on a fine balance made among excitatory and inhibitory dopamine transmission (21-23). Dopamine levels are peaking during adolescence in prefrontal cortex, versus childhood or adulthood in non-human primates (24). The consequences of this unsynchronized development relates to adolescents being able to make good decisions in so called "cold" cognition situations, where there is no or little arousal and intense emotion. However, in "hot" cognition situations, where intense emotion and arousal is present, teens tend to make poorer decisions (3). This may be associated to the known fact that adolescents engage in risky behavior, often due to the influence of feelings, emotions and peers (25, 26).

The neurobiological model of adolescence, proposed by Casey et al. (6), suggests that the adolescent is capable of making rational decisions; however, when it comes to the emotionally charged situations, the more mature limbic system dominates over the less mature prefrontal cortex. Not only do the adolescents show stronger emotional response to "hot" cognition situations, but what is more, they often do not correctly identify emotion of other people involved. To map the differences between teen and adult brain, the volunteer participants were shown series of pictures while their brain was scanned through MRI, and were asked to recognize the emotion on series of faces (27). While 100% of adults correctly recognized fear, 50% of adolescents misinterpreted fear for sadness, shock or anger. At the same time, MRI scans showed that teenagers were using less the prefrontal (upper) region than adults while reading emotions of the faces they were shown. This, again, confirms that the executive region of the brain, the frontal lobe, is not functioning fully in teenagers, resulting in poor thinking through the actions that define their behavior (6).

The neurotransmitters - dopamine, serotonin and melatonin, are thought to play a crucial role in the maturation of adolescent behavior (3). The dopamine is associated with movement, the ability to experience pleasure and the emotional responses, and its decline during adolescence may lead to mood swings and difficulties in emotion regulation (3). The serotonin is responsible for regulating mood alternations, anxiety, impulse control and arousal (5, 28), and its drop during adolescence may be associated with poor impulse control (3). Melatonin is in charge of the circadian rhythms, the sleep–wake cycle, and the necessity of sleep during adolescence (3), and some contemporary research data point out to the specific decrease of this neurotransmitter during puberty (29).

Corpus Callosum and Cerebellum Development during Adolescence

While adolescents are gaining new abilities through the development of their executive skills, and more control over their limbic system through the development of their prefrontal cortex, the analyses of corpus callosum have shown that adolescence is a period of losing some abilities as well (30). Increased activity of prefrontal region as an indication of maturation and diminished activity in irrelevant brain regions are proposed as the neurobiological explanation of the behavioral changes associated with adolescence (9). These findings are in accord with the studies on language acquisition that show that the ability to learn new languages declines some time after the age of 12 (31).

An accelerated growth of callosum isthmus suggests the development of networks that support the associative reasoning and language functions after children enter school (although not immediately after the start of formal education). The peak growth occurring at about the age of 12, supports the hypothesis "that there is a critical period for first-language acquisition that ends at puberty, if not before" (32). The continuing growth of the callosal isthmus, up until the age of 15-16, stays in line with previously reported growth foci in linguistic callosal regions, in subjects aged from 6-15 (32) and may reflect fine tuning of language functions which are known to occur late in childhood. Finally, at the age of 17, the isthmus starts to slowly decrease, probably due to pruning of fibers that connect auditory and speech systems. Any pruning indicates a decreased inter-hemispheric communication, perhaps due to language functions being more lateralized at the age of 17-18 than before (30). This assumption complies with the outcomes of functional analyses indicating that language lateralization increases between the age of 5-20, reaching plateau between 20-25, and slowly decreases between 25-70 years (33).

Another section of neuroanatomy, the cerebellum, is very different in twins, leading to hypothesis that the cerebellum is not genetically controlled but susceptible to the environment (34, 35). Interestingly, the cerebellum is a part of the brain that changes during whole adolescence. The cerebellum helps in physical coordination, however, looking at functional imaging studies of the brain, the researchers also see its activities during mental tasks (36). Cerebellum is like a math co-processor. It is not essential for any activity, but it does make every activity better. Any high-order thought-process, such as: mathematics, music, philosophy, decision-making, social skills - draws upon the cerebellum (36). Navigating the complicated social life of the teens without stumbling - seems to be a function of the cerebellum as well (36).

The Role of Gender Differences in Functional Brain Development during Puberty as Measured by fMRI

A number of adult and adolescent functional MRI (fMRI) studies show gender differences in neural activity in a range of cognitive paradigms, and some gender di-

fferences may be due to prenatal sex hormone effects, to puberty-independent effects of genes encoded on the sex chromosomes, or to gender-specific environmental effects across the lifetime (10). Animal studies have shown that hormones such as testosterone, estrogen and progesterone are critical for myelination studies (38). The results suggest that ovarian hormones may enhance cortical and subcortico-cortical functional and structural connectivity, whereas testosterone decreases subcortico-cortical connectivity, but increases connectivity between subcortical areas (37).

Several fMRI studies have been conducted in populations with endocrine dysfunctions. Although the results are difficult to interpret with regards to typical puberty and adolescence, since these populations are hormonally abnormal prior to puberty onset, they still provide converging evidence that determinants or correlates of puberty influence functional brain activity (10). A fMRI study by Mueller et al. (38) analyzed the brain activity during a facial emotion-processing task between adolescent males with familial hyperandrogenism (causing excess testosterone from an early age). Relative to controls, the group with excess testosterone presented elevated hippocampal activity during fear processing, as well as faster behavioral responses to faces showing fearful expressions. In an fMRI study by Ernst et al. (39), seven male and seven female adolescents with congenital adrenal hyperplasia (resulting in excess testosterone in utero) were compared with age and gender-matched controls in a similar facial emotion processing task. In contrast to the study by Mueller et al, no group differences were reported in the hippocampus. However, in the female clinical group, the enhanced amygdala activity during fear and anger processing was noticed, relative to female controls. The enhanced amygdala activity in the female clinical group was similar to that in male controls, which suggests a mediating effect of testosterone.

Conclusion

Adolescence is a period of profound transition in terms of drives, emotions, motivations, psychology and social life. Preliminary evidence from developmental MRI studies has suggested that the stage of puberty plays an important role in adolescent brain development. There is a great value in better understanding of the relationships between the brain, cognition, behavior, and puberty in terms of prevention of risk taking behavior in adolescents. Exuberant growth during pre-pubertal period gives the brain an enormous potential. We are just beginning to understand is the influence of: parenting, teaching, society, nutrition, infections and other factors on this building-up phase. The phase of pruning mirrors the ”use it or lose it“ principle – the cells and synapses that are being used will flourish, while those that are not used will eventually die. It shows that time around puberty and on into adult years is a critical time for brain developing, especially for parts of brain cortex that controls organizational skills and decision making.

There is still a long way to go in our search, in order to understand the biological underpinnings of mental health disorders, especially those originated in adolescent period. Further research is needed to discover how hormones influenced the development of brain structure and function. It is essential to achieve the better understanding of the relationships between the brain, cognition, behavior and puberty.

Reference

1. Jean MT. Generation me: why today's young Americans are more confident, assertive, and entitled—and more miserable than ever before. New York: Free Press, 2006.
2. Stevens R. Erik Erikson: An Introduction. New York, NY: St. Martin's Press, 1983. pp. 48–50.
3. Arain M, Haque M, Johal L, Mathur P, Nel W, Rais A, et al. Maturation of the adolescent brain. Neuropsychiatr Dis Treat. 2013; 9: 449–461
4. Jay NG, Jonathan B, Neal OJ, Castellanos FX, Hong L, Alex Z et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999;2(10):861-863.
5. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann NY Acad Sci. 2004; 1021:77-85.
6. Casey BJ, Galvan A, Hare TA. Changes in cerebral functional organization during cognitive development. Curr Opin Neurobiol 2005; 15(2):239-244.
7. Frontline: Inside the Teenage Brain. Available from http://www.pbs.org/wgbh/pages/frontline/shows/teenbrain/
8. Giedd JN. The amazing teen brain. Sci Am. 2015; 312(6):32-37.
9. Blakemore SJ, Burnett S, Dahl RE. The role of puberty in the developing adolescent brain. Hum Brain Mapp. 2010; 31(6): 926–933.
10. Cahill I. Why sex matters for neuroscience. Nat Rev Neurosci. 2006; 7:477-484.
11. Casey BJ, Galvan A, Hare TA. Changes in cerebral functional organization during cognitive development. Curr Opin Neurobiol 2005; 15(2):239-244.
12. Dorn LD. Measuring puberty. J Adolesc Health. 2006; 39:625-626.
13. Schulz KM, Molenda-Figueira HA, Sisk CL. Back to the future: the reorganizational-activational hypothesis adapted to puberty and adolescence. Horm Behav. 2009;55:597-604.
14. Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb Cortex 2010; 20:534-548.
15. Whitaker KJ, Vértes PE, Romero-Garcia R, Váša F, Moutoussis M, Prabhu G et al. Adolescence is associated with gnomically patterned consolidation of the hubs of the human brain connectome. Proc Natl Acad Sci U S A. 2016;113(32):9105-9110.

16. Li K, Xu E. The role and the mechanism of gamma-aminobutyric acid during central nervous system development. Neurosci Bull. 2008; 24(3):195-200.
17. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav. 2007 Feb;86(2):189-99.
18. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol. 2002;453(2):116–130.
19. Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology. 2004;29(11):1988–1993.
20. Teicher MH, Andersen SL, Hostetter JC., Jr Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res Dev Brain Res. 1995;89(2):167–172.
21. Floresco SB, Tse MT. Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala-prefrontal cortical pathway. J Neurosci. 2007;27(8):2045–2057.
22. Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 2007;30(5):220–227.
23. Jackson ME, Frost AS, Moghaddam B. Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J Neurochem. 2001;78(4):920–923.
24. Rosenberg DR, Lewis DA. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemically analysis. J Comp Neurol. 1995;358(3):383–400.
25. Gardener M, Steinberg L. Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. Dev Psych. 2005;41:625–635.
26. Steinberg L. Cognitive and affective development in adolescence. Trends Cogn Sci. 2005;9(2):69–74.
27. Killgore DS, Yurgelun-Todd DA. Cerebral correlates of amygdala responses during non-conscious perception of facial affect in adolescent and pre-adolescent children. Cogn Neurosci. 2010;1(1):33–43.
28. Wahlstrom D, Collins P, Whit T, Luciana M. Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. Brain Cogn. 2010; 72(1):146-159.
29. Crowley SJ, Acebo C, Carskadon MA. Human Puberty: Salivary Melatonin Profiles in Constant Conditions. Dev Psychobio. 2012;54(4):468-473.
30. Luders E, Thompson PM, Toga AW. The development of the corpus callosum in the healthy human brain. J Neurosci. 2010;30(33): 10985–10990.
31. Grimshaw GM, Adelstein A, Bryden MP, MacKinnon GE. First-language acquisition in adolescence: evidence for a critical period for verbal language development. Brain Lang. 1998;63:237–255.
32. Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature. 2000;404:190–193.
33. Szaflarski JP, Holland SK, Schmithorst VJ, Byars AW. fMRI study of language lateralization in children and adults. Hum Brain Mapp. 2006;27:202–212.
34. Gilmore JH, Schmitt JE, Knickmeyer RC, Smith JK, Lin W, Styner M et al. Genetic and environmental contributions to neonatal brain structure: a twin study. Hum Brain Mapp. 2010;31(8):1174-82
35. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. Neuroimage. 2009;44(2):489-501.
36. Leinera HC, Leinera AL, Dowb RS. Cognitive and language functions of the human cerebellum. Elsevier Ltd., 1993.
37. Peper JS, van den Heuvel MP, Mandl RC, Hulshoff Pol HE, van Honk J. Sex steroids and connectivity in the human brain: a review of neuroimaging studies. Psychoneuroendocrinology. 2011;36(8):1101-1113.
38. Mueller SC, Mandell D, Leschek EW, Pine DS, Merke DP, Ernst M. Early hyperandrogenism affects the development of hippocampal function: Preliminary evidence from a functional magnetic resonance imaging study of boys with familial male precocious puberty. J Child Adolesc Psychopharmacol. 2009;19:41–50.
39. Ernst M, Maheu FS, Schroth E, Hardin J, Golan LG, Cameron J et al. Amygdala function in adolescents with congenital adrenal hyperplasia: A model for the study of early steroid abnormalities. Neuropsychologia. 2007;45:2104–2113.