Journal of Adolescent Health 52 (2013) S7–S13

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Review article

Adolescent Neurodevelopment

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Article history: Received January 22, 2012; Accepted May 23, 2012

Keywords: Adolescence; Brain; Neurodevelopment; Brain imaging; Cognitive control; Reward sensitivity; Aversive stimuli; Emotions; Risk taking; Public policy

A B S T R A C T

Purpose: The purpose of this article is to outline notable alterations occurring in the adolescent brain, and to consider potential ramifications of these developmental transformations for public policy and programs involving adolescents.

Methods: Developmental changes in the adolescent brain obtained from human imaging work are reviewed, along with results of basic science studies.

Results: Adolescent brain transformations include both progressive and regressive changes that are regionally specific and serve to refine brain functional connectivity. Along with still-maturing inhibitory control systems that can be overcome under emotional circumstances, the adolescent brain is associated with sometimes elevated activation of reward-relevant brain regions, whereas sensitivity to aversive stimuli may be attenuated. At this time, the developmental shift from greater brain plasticity early in life to the relative stability of the mature brain is still tilted more toward plasticity than seen in adulthood, perhaps providing an opportunity for some experience-influenced sculpting of the adolescent brain.

Conclusions: Normal developmental transformations in brain reward/aversive systems, areas critical for inhibitory control, and regions activated by emotional, exciting, and stressful stimuli may promote some normative degree of adolescent risk taking. These findings have a number of potential implications for public policies and programs focused on adolescent health and well-being.

Development of the brain is far from complete at the time of birth, with maturation continuing through childhood and adolescence, and even some age-related changes in brain organization and function (including the generation of modest numbers of brain cells) into adult life [1]. Studies conducted over the past several decades have revealed adolescence as a time of particularly notable morphological and functional transformations in the brain that, along with increasing hormone levels and other biological changes, interact with cultural, economic, and psychosocial forces to shape how adolescents think, feel, and behave [2]. The purpose of this article is to outline some of the more notable alterations occurring in the adolescent brain, and briefly consider some potential ramifications of these normal developmental transformations for public policies and programs involving adolescents.

Understanding of adolescent brain development continues to escalate rapidly, aided considerably by increasingly informative insight into normal developing human brains provided by continued improvements in imaging technologies. Magnetic resonance imaging (MRI) and other imaging technologies have proved valuable for detailing the size of [3,4] and connectivity across [5,6] brain regions at different ages, as well as for indexing relative changes in regional activation patterns during performance of target risk taking, decision making, or other tasks [7]. However, space and movement constraints limit task-related responses possible within scanners, making it a challenge to relate these findings to the social and emotionally arousing situations in which adolescents often engage in risky behavior. Dissecting causal relationships and the precise morphological and molecular underpinnings of observed age differences typically requires approaches and levels of analyses largely unavailable

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1054-139X
http://dx.doi.org/10.1016/j.jadohealth.2012.05.006

with imaging, but more amenable to study using animal models of adolescence. Although the human brain and the behavior it supports are far more complex than those of other species, relevance of research using simple mammalian models of adolescence is aided by considerable across-species similarities in behavior and biology seen between humans and other mammalian species. The basics of brain structure and function arose millions of years ago, and the relative timing of regional brain development has been evolutionarily conserved as well [8]. Common behavioral proclivities seen in human adolescents and their counterparts in other species include elevations in peer-directed social interactions along with occasional increases in fighting with parents [9–11], increases in novelty seeking, sensation seeking, and risk taking [12–15], and greater per-occasion alcohol use [16,17]. These across-species similarities support the suggestion that certain neurobehavioral characteristics of adolescence may be tethered in part by biological roots embedded in the evolutionary past [18].

Recent Advances in Understanding of Adolescent Brain Development

Synaptic pruning and myelination

Brain development is a mix of expansion and regression. Many more brain cells specialized for processing and transmitting information (neurons) and their synaptic connections are produced than will ultimately be retained [19,20]. This overproduction and pruning are thought to ensure that appropriate connectivity is established, with neurons and synapses that fail to make appropriate connections being lost [21]. Although such regressive processes are most prevalent during early brain development, they continue to some extent throughout life, with synaptic pruning, in particular, being a hallmark of the brain transformations of adolescence. Pruning during adolescence is highly specific and can be pronounced, resulting in a loss of approximately 50% of the synaptic connections in some regions, but with little decline in others [21]. Pruning has been speculated to help with the "rewiring" of brain connections into adult-typical patterns, and could potentially represent relatively late opportunities for brain plasticity, as discussed later in the text. Synapses are energetically costly, and declines in their numbers likely contribute to the increases in brain efficiency seen during adolescence, reflected by the declines in brain energy use seen through adolescence in humans and other species [22,23].

Not all brain changes during adolescence are regressive, with some neurons continuing to grow processes and establish new synaptic connections [1]. There are also major shifts in the speed and timing of information flow across the brain that influence functional connectivity across brain regions during adolescence [24]. Speed and efficiency of information flow across relatively distant regions are accelerated during adolescence because neuronal axons interconnecting certain brain areas become insulated with a white, fat-enriched substance called myelin, thereby markedly increasing the speed of electrical transmission along axons and at the same time reducing the energy needed to maintain this process. Although myelination begins early in life and continues into adulthood, its production escalates notably during adolescence [25], thereby speeding information flow across distant regions and magnifying its impact [26].

These processes of myelination and synaptic pruning help to reconfigure brain connectivity into the adult form and are thought to contribute to the developmental "thinning" that occurs in the neocortex, that is, the decline in thickness of outer layers of the brain that are most evolutionarily advanced in humans and are thought to play particularly important roles in higher levels of information processing and orchestrating actions. The thinning of cortical "gray matter" regions enriched in neurons, synapses, and support cells with maturation may be related not only to declines in the number of synaptic processes but also to increases in myelinated "white matter" tracts that pass underneath cortical gray matter, decreasing relative gray matter to white matter volume [27].

Regional specificity, changes in connectivity, and refinement of networks

Cortical development generally proceeds in "waves," with the timing of gray matter thinning occurring well before adolescence in cortical regions involved in basic sensory and motor function, whereas thinning continues throughout adolescence in prefrontal cortex (PFC) and other frontal cortical regions implicated in advanced cognitive functions. Development in noncortical areas is also thought to contribute to adolescent-characteristic behaviors. Subcortical regions receiving notable attention, which will be reviewed later in the text, include areas modulating social, aversive, and emotional stimuli, such as the amygdala, and regions implicated in the processing of rewarding stimuli, as exemplified later by neurons releasing the neurotransmitter dopamine (DA) and regions receiving this input, such as the ventral striatum. Developmental changes in these areas will be considered in conjunction with cognitive and behavioral data to support the suggestion that enhanced proclivities for risk taking, sensation seeking, and alcohol/drug use often seen during adolescence are influenced in part by immature cognitive control capacities, which can be overwhelmed by enhanced reactivity (and perhaps cross-reactivity) to social and emotional stimuli and to rewards under certain circumstances, along with sometimes attenuated reactivity to aversive stimuli/consequences.

However, development of the brain is not simply a chronology of developmental immaturities, with different areas coming online at different times. Rather, contemporary views of brain maturation consider it to be a dynamic process by which separate networks of functionally related regions become more strongly linked over time [24,28,29] via weakening connections between different networks while intensifying within-network connections, particularly those linking more distant network regions [30]—the latter presumably aided by the preferential myelination of longer axonal tracts as discussed previously. Such increases in network cohesion may contribute to developmental changes in patterns of brain activation, with activation in task-relevant regions often becoming less diffuse and more focal (distinct) with development [31].

Prefrontal areas and development of cognitive control

Theories of adolescent brain development generally concur on the importance of delayed maturation of the PFC and other frontal regions for developmental immaturities in cognitive control, attentional regulation, response inhibition, and other relatively advanced cognitive functions [7]. Although youth can perform well on tasks tapping these cognitive functions under certain conditions, performance impairments often emerge with increases in task demands, or under conditions of heightened

arousal and emotions. Indeed, stressful and emotionally arousing situations have been shown to attenuate activity in PFC and other frontal regions [32], and at the same time to increase activity in subcortical regions modulating emotional reactivity, such as the amygdala, as discussed later in the text.

Evidence for delayed maturation of frontal regions is evident in terms of cortical thinning [33], as well as via switches from more diffuse to greater focal activation of frontal regions during performance on tasks requiring inhibitory self-control [31,34]. Maturation of inhibitory control during adolescence is also associated with increasing involvement of frontal/PFC regions within networks linking these control regions with other areas [35,36]. Development of frontal regions into late adolescence/early adulthood is thought to result in relatively late maturation of "top-down" control systems that gradually strengthen their control over early emerging, largely subcortical "bottom-up" systems that are highly responsive to rewarding and emotional stimuli [7]. Development of these "bottom-up" systems will be considered next.

DA, the ventral striatum, and adolescent-related alterations in reward sensitivity

Novel stimuli, exciting and risky situations, and alcohol, nicotine, and other drugs of potential abuse tap into complex and ancient brain reward circuitry that is critical for seeking, finding, and "consuming" survival-essential natural rewards such as food, water, warmth, sexual partners, and other social stimuli [37]. This reward circuitry includes the DA neurotransmitter system and its projections to reward-relevant subcortical regions, such as the ventral striatum [38]. As examples of these marked transformations, in some reward-relevant areas, there is a loss of up to 50% of some types of receptors that are necessary to respond to DA, whereas in other areas, ongoing levels of DA activity may increase two- to sevenfold during adolescence [39,40].

Consistent with the diversity and complexity of the developmental transformations in these reward-relevant regions, evidence is mounting rapidly that these areas respond differently to rewarding stimuli during adolescence than in adulthood, although the age differences observed are complex. On one hand, adolescents sometimes [41–43], although not always [44], show greater activation in ventral striatum while receiving rewards than do children or adults. Type of task, context, and reward intensity might contribute to differences seen across studies [45], with adolescents, for instance, found to show greater ventral striatum responses to larger rewards but weaker responses to relatively small rewards [41]. In contrast to the sometimes exaggerated ventral striatum responses to rewards, adolescents often show a reduced ventral striatal response when anticipating a reward or when shown cues predicting the reward [44,46]. Ostensibly, these data might seem counter to the avidity with which adolescents pursue rewards. Yet, attenuated activations of ventral striatum during reward anticipation are associated with greater risk-taking biases among adolescents [47] and with elevated levels of impulsivity among alcoholics compared with a group of adult control subjects [48]. Thus, attenuated ventral striatal activation during reward anticipation may normally be evident to some extent among adolescents, with this insensitivity to anticipatory activation particularly pronounced among adolescents with stronger propensities for risk taking, perhaps serving as a risk factor for later problematic alcohol/drug use.

Consistent with adolescent-typical alterations in reward-relevant brain regions and reminiscent of the sometimes heightened ventral striatal response of adolescents to the receipt of rewards, behavioral sensitivity to rewards has often been reported to peak during adolescence. For instance, reward seeking (indexed via self-report or sensitivity to positive feedback in a gambling task) was found to increase and peak in midadolescence (i.e., approximately 14–15 years) and then to gradually decline into adulthood [15,49,50]. Even sensitivity to a basic reward—sweet substances—was likewise higher at this time (11–15 years of age) than during late adolescence and emerging adulthood (19–25 years) [51]. Data supporting a strong biological component to this enhanced reward responsivity have been obtained using simple animal models, with adolescent rats likewise often found to be more sensitive than adults to the rewarding properties of stimuli, which range from desirable tastes, social peers, and novelty, to drugs of abuse, including cocaine, amphetamine, nicotine, and alcohol [38].

Neurobehavioral response of adolescents to aversive stimuli

Aversive stimuli and negative consequences typically signal dangerous circumstances, with various regions throughout the brain sensitively responding to such stimuli. Adolescents often appear less "harm avoidant" than adults when indexed via neural responding to aversive stimuli, threats, and penalties [52]. For instance, the amygdala of adolescents is activated less than that of adults in response to aversive outcomes (reward omission) [52]. Likewise, a region of frontal cortex that monitors penalties and conflict was activated by the threat of both mild and high penalties in adults, but only by the threat of high penalty in adolescents, suggesting that this area is less sensitive to penalties in adolescents than adults [53]. These data are consistent with other emerging evidence that neural responses to negative feedback may mature later than responses to positive feedback [54,55].

A reduced responsiveness to aversive stimuli during adolescence is often [50,56,57], although not always [58], evident behaviorally. For instance, sensitivity to negative feedback in a gambling task was found to be low during early to midadolescence, and to increase gradually thereafter [50,57]. Similar behavioral findings have emerged in animal studies, supporting a biological basis for adolescent insensitivities to aversive stimuli. For instance, adolescent rats are often less sensitive than adults to aversive properties of both nondrug and drug stimuli, with the latter emerging at higher doses of the same drugs that, at lower doses, they conversely find more reinforcing than adults (cocaine, amphetamine, nicotine, and alcohol) [38,59,60]. In the case of alcohol, this adolescent insensitivity includes various intoxicating effects of alcohol, such as motor incoordination, social impairment, and sedation—effects likely serving as cues to moderate intake [61]. Adolescent-typical insensitivities to aversive stimuli in the presence of greater reward sensitivity could contribute to the proclivity of adolescents to associate more benefit and less cost to alcohol and drug use, as well as other risk behaviors [62].

The amygdala, social behavior, and "hot" cognitions

There is considerable overlap between systems processing aversive stimuli and those responsive to emotions and social stimuli, such as the amygdala. Indeed, aversive stimuli often

produce negative emotions, and social stimuli are exquisitely effective in inducing both positive and negative emotions. Given the often heightened emotionality and peer focus of adolescents, developmental studies have frequently assessed activation of the amygdala to emotional (often fearful) faces relative to neutral faces. In some [63,64], but not all [65], studies, adolescents were found to exhibit greater amygdala activation to emotional faces than adults (and children, when studied), with data supporting the suggestion that adolescents show increased neural reactivity to emotional properties of social stimuli.

This social/emotional bias may alter attention to other situational or task features. For example, greater amygdala activation to emotional faces was correlated with slower reaction times during performance of a response inhibition task that used these faces as stimuli [64]. Indeed, although the rational decision making of adolescents reaches adult-typical levels by midadolescence, this capacity can be reduced under stressful, emotionally charged, and arousing circumstances [49]—a phenomenon called "hot cognitions" [66]. For instance, when both emotional and nonemotional versions of a risk-taking task were examined, adolescents exhibited more risk-taking behavior than adults only under the emotional version of the task [67]. Social peers seem particularly effective in inducing "hot" emotional states during adolescence, with adolescents showing markedly more risk taking than adults when tested in a computerized risk-taking task in the presence of peers; however, this was not the case when individuals at both ages were tested alone [68]. Adolescent engagement in risky behaviors commonly occurs in social situations [57].

Adolescent brain plasticity

As an organ specialized for processing and using information to modify cognitions and behavior, the brain must maintain some degree of functional stability while still being sufficiently malleable to adapt to new experiences throughout life. The balance between plasticity and stability is tilted toward plasticity early in life, a time when there are many opportunities for the brain to be sculpted by experiences ranging from initial sensory experiences to early nutrient exposure/restriction or developmental adversities [69–71]. At maturity, the balance is shifted toward greater stability of neural circuits, although the capacity for plasticity is still present in a restricted form [72]. There is evidence that some heightened developmental plasticity extends into adolescence, thereby potentially providing a relatively late opportunity for the brain to be customized to match the activities and experiences of the adolescent. Whether this adolescent brain plasticity is unique or merely reflects an intermediate transition in the developmental shift from the heightened neural plasticity seen early in life to the greater neural stability of the mature brain is yet unknown and may vary with the brain systems and functions under investigation, as well as the stimuli precipitating adaptations in these systems. Effective stimuli may include not only the environment and experiences of the adolescent but pubertal hormones as well. Increases in gonadal steroids (e.g., estrogen, testosterone) at puberty have been shown to influence maturation of brain regions critical for reproductive behavior, thereby helping to program sex-typical responses to gonadal hormones in adulthood [73].

Likely neural targets for experience-related plasticity during adolescence may be developmental transformations normally occurring in the brain at this time. Synapses in the adolescent brain are notably more dynamic than they are in adulthood, with axons growing and retracting and new synapses being formed and others eliminated at notably greater rates than seen in the mature brain [74,75]. Some of the synaptic pruning that is seen during adolescence appears in part experience dependent [75], as does the process of myelination, with axonal myelination driven partly by the amount of electrical activity passing along to-be-myelinated axons [76]. Findings consistent with experience-dependent myelination are beginning to emerge from human imaging studies as well. For instance, in a study of professional musicians, the amount of white matter development in performance-relevant tract pathways was correlated with the amount of time spent practicing, especially practice time during childhood and during early/midadolescence [77]. Myelination is thought to be one of the negative regulators of plasticity, raising the possibility that experience-related increases in myelination may serve to stabilize relevant axonal pathways at the cost of their further plasticity [78].

Basic science studies have also revealed evidence for 4–5 times higher rates of formation of new neurons during adolescence than in adulthood [79]. Formation of modest amounts of new neurons throughout life is restricted to a few brain regions, but is thought to be important for some forms of learning, for repair after brain damage, and as one possible mediator of beneficial effects of exercise and enriched environments [80]. Such beneficial effects have been seen after exposures during adolescence [81] and in adulthood [82], although studies have yet to include age comparisons to determine whether the brain of the adolescent is more sensitive to these effects than the adult brain.

Indeed, finding that the adolescent brain is sensitive to environmental manipulations is not the same as showing that adolescence represents a critical period, or time of special vulnerability and opportunity, for brain plasticity. For at least some kinds of experiences, it is possible that similar brain plasticity might extend into adulthood. However, even if adolescence does not represent a critical period for neuroplasticity, it is possible that environmental experiences might prove particularly critical for altering trajectories away from or toward certain problematic outcomes at this time of relatively rapid neural, behavioral, and cognitive change.

Broad implications of recent research for adolescent policy and programs

It is a leap from the science of adolescent brain development to public policy, particularly given that most relevant data are derived from human imaging studies that largely do not address causal or mechanistic relationships, or from research using simple animal models whose relevance to human adolescents often remains to be established. Nevertheless, converging data and emerging consensus in certain instances may be sufficient to help inform adolescent policy discussions.

Adolescents often seem to view rewarding and aversive stimuli differently than adults do, showing a shift toward enhanced sensitivity to rewards but attenuated aversive sensitivities that may extend to alcohol and other drugs. Such hedonic shifts could encourage the pursuit of, continued engagement in, and escalation of risky and exciting activities, particularly when previous activities proved rewarding and without disastrous consequences. Indeed, risk taking has been viewed as "one dimension of the drive for thrills and excitement" [83, p.296]. Attenuated aversive consequences in the face of a potential for greater re-

warding benefits could combine with genetic and environmental risk factors to promote relatively high levels of reward "consumption," leading to problematic involvements with alcohol, other drugs, or other rewarding or risky stimuli.

Turning to potential policy ramifications, evidence for enhanced sensitivity to strong rewards during adolescence could be used to support policies to limit access to or discourage excessive use of highly rewarding substances during adolescence (e.g., pricing elevations; age restrictions to limit access to cigarettes, alcohol, and gambling; restricting availability of high-caloric/low-nutritional capacity food and drinks in schools). In contrast, taking into account consideration of adolescent-associated attenuations in aversive sensitivity, policies could be developed to help insulate and scaffold adolescents in risky situations that include exploration of negative experiences, given that adolescents are perhaps less likely to attribute negative outcomes to those experiences [56].

Context plays a particularly dramatic role in influencing adolescent behavior, with stressful, exciting, and emotionally arousing circumstances not only increasing activity in subcortical regions modulating reactivity to socioemotional and rewarding stimuli, but also attenuating activity in the frontal cortical regions critical for logical thinking and cognitive control, thereby promoting "hot cognitions" and potentially leading to risky activities. Such findings have been used to support different ages for informed consent under conditions favoring "cold" cognitions versus for culpability to illegal acts occurring under conditions favoring "hot" cognitions [84]. Adolescent-typical proclivities for developing hot cognitions also could be used to support policies to restrict the access of adolescents to contexts that are particularly likely to promote risky behaviors. Graduated driving licenses are but one example.

Programs to reduce stress levels within typical contexts of adolescence could be promoted to help adolescents increase their capacity to cope with stressors and reduce their propensity to exhibit "hot cognitions." Recent data demonstrating that sleep deprivation likewise shifts brain activation toward "hot cognitions" [85], taken together with evidence for a partially biologically driven phase shift toward delayed sleep onset and later awakening that usually leads to some sleep deprivation during the school week [86], could serve to add further impetus to policies shifting to later school start times for adolescents than younger individuals.

Adolescent-typical ways of thinking and behaving appear in part neurobiologically based. Given such strong biological roots, it perhaps should not be surprising that some degree of sensation seeking and risk taking is often normative during adolescence [57] and perhaps even rational under some circumstances [56]. Rather than trying to eliminate adolescent risk taking via abstinence programs or training in social skills or social norms—strategies that have not proved successful to date [57]—a better tactic might be to reduce the costs of adolescent risk taking by limiting access to particularly harmful risk-taking situations, while perhaps providing opportunities to engage in risky and exciting activities under circumstances designed to lessen changes for harm.

Recommendations for future research

One critical area for future research is that of individual differences and the degree to which adolescent neurobehavioral function is influenced by genetic background and previous experiences. Many youth traverse adolescence relatively easily, with their risk-taking behaviors limited and without notable adverse consequences (sometimes perhaps more by happenstance than design). However, for other individuals, adolescent behavioral choices have severe consequences, including lasting alcohol/drug abuse, incarceration, or even death, with mortality rates increasing two- to fourfold during the otherwise healthy adolescent period [87]. For some adolescents, adjustment problems may evolve into psychological disorders, with increases in the incidence of a variety of disorders during adolescence [88]. Little is known of how development of the adolescent brain influences expression of individual differences across the course of adolescence, or of the role of environmental experiences in the emergence of resiliencies and vulnerabilities among individual adolescents. Additional knowledge of individual variation in such resiliencies/vulnerabilities (and how to detect these using behavioral or biomarkers) is essential for developing individually targeted prevention and intervention strategies that are likely to be more beneficial than more broad-based strategies aimed at large populations of adolescents.

Another exciting area for future research with significant policy implications is the issue of adolescent brain plasticity. Although it is clear that environmental circumstances of the adolescent matter, and that the maturing brain during adolescence is sensitive to these experiences, many critical questions remain:

a. To what degree do adolescent experiences (including those provided by adolescent risk-taking) customize the maturing brain in ways commensurate with those experiences?
b. What experiences are effective, how much experience is necessary, and to what degree are these experience-dependent adaptations beneficial or detrimental?
c. How long lasting are these effects?
d. Can the plasticity of adolescent brain be "exploited" to train adolescents to enhance their self-control under emotional circumstances, or to accelerate neural maturation of regions critical for cognitive control? If such training is effective, would training to minimize the natural course of adolescence be advisable?
e. And, importantly, does adolescence represent a critical period for experience-dependent brain sculpting, or does this plasticity merely reflect a capacity for neuroadaptations that continues relatively unabated throughout life?

Answers to questions such as these will help determine the degree to which communities, schools, and families should focus efforts to promote specific contexts and experiences for adolescents while discouraging others. Even modest adjustments of developmental trajectories that are slightly offtrack during adolescence may yield substantially more benefit than waiting until those trajectories have diverged considerably later in life.

Acknowledgments

Preparation of this review was supported in part by NIH grants U01 AA019972, P50 AA017823, R01 AA018026, R01 AA017355 and R01 AA 016887.

References

[1] de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: What is happening when? Early Hum Dev 2006;82:257–66.

[2] Spear L. The Behavioral Neuroscience of Adolescence. New York, NY: Norton, 2010.
[3] Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 2006;30:718–29.
[4] Shaw P, Greenstein D, Lerch J, et al. Intellectual ability and cortical development in children and adolescents. Nature 2006;440:676–9.
[5] Asato MR, Terwilliger R, Woo J, Luna B. White matter development in adolescence: A DTI study. Cereb Cortex 2010;20:2122–31.
[6] Biswal BB, Mennes M, Zuo XN, et al. Toward discovery science of human brain function. Proc Natl Acad Sci U S A 2010;107:4734–9.
[7] Casey BJ, Getz S, Galvan A. The adolescent brain. Dev Rev 2008;28:62–77.
[8] Allman JM. Evolving Brains. New York, NY: Scientific American Library, 2000.
[9] Csikszentmihalyi M, Larson R, Prescott S. The ecology of adolescent activity and experience. J Youth Adolesc 1977;6:281–94.
[10] Primus RJ, Kellogg CK. Pubertal-related changes influence the development of environment-related social interaction in the male rat. Dev Psychobiol 1989;22:633–43.
[11] Steinberg L. Pubertal maturation and parent-adolescent distance: An evolutionary perspective. In: Adams GR, Montemayor R, Gullotta TP, eds. Advances in Adolescent Behavior and Development. Newbury Park, CA: Sage Publications, 1989:71–97.
[12] Adriani W, Chiarotti F, Laviola G. Elevated novelty seeking and peculiar d-amphetamine sensitization in periadolescent mice compared with adult mice. Behav Neurosci 1998;112:1152–66.
[13] Trimpop RM, Kerr JH, Kirkcaldy B. Comparing personality constructs of risk-taking behavior. Pers Individ Dif 1999;26:237–54.
[14] Romer D, Duckworth AL, Sznitman S, Park S. Can adolescents learn self-control? Delay of gratification in the development of control over risk taking. Prev Sci 2010;11:319–30.
[15] Steinberg L. A dual systems model of adolescent risk-taking. Dev Psychobiol 2010;52:216–24.
[16] Doremus TL, Brunell SC, Rajendran P, Spear LP. Factors influencing elevated ethanol consumption in adolescent relative to adult rats. Alcohol Clin Exp Res 2005;29:1796–808.
[17] SAMHSA. Results from the 2005 national survey on drug use and health: National findings. In: National Survey on Drug Use and Health Series H-30, DHHS publication SMA 06-4194. Rockville, MD: DHHS, 2006.
[18] Spear LP. Neurobehavioral abnormalities following exposure to drugs of abuse during development. In: Johnson BA, Roache JD, eds. Drug Addiction and its Treatment: Nexus of Neuroscience and Behavior. Philadelphia, PA: Lippincott-Raven Publishers, 1997:233–55.
[19] Oppenheim RW. Cell death during development of the nervous system. Annu Rev Neurosci 1991;14:453–501.
[20] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387:167–78.
[21] Rakic PBourgeois JPGoldman-Rakic PS. Synaptic development of the cerebral cortex: Implications for learning, memory, and mental illness. In: van Pelt J, Corner MA, Uylings HBM, Lopes FH, eds. The Self-Organizing Brain: From Growth Cones to Functional Networks Vol 102. Amsterdam, the Netherlands: Elsevier Science, 1994:227–43.
[22] Chugani HT. Neuroimaging of developmental nonlinearity and developmental pathologies. In: Thatcher RW, Lyon GR, Rumsey J, Krasnegor N, eds. Developmental Neuroimaging: Mapping the Development of Brain and Behavior. San Diego, CA: Academic Press, 1996:187–95.
[23] Tyler DB, van Harreveld A. The respiration of the developing brain. Am J Physiol 1942;136:600–3.
[24] Fair DA, Cohen AL, Dosenbach NU, et al. The maturing architecture of the brain's default network. Proc Natl Acad Sci U S A 2008;105:4028–32.
[25] Lu LH, Sowell ER. Morphological development of the brain: What has imaging told us? In: Rumsey JM, Ernst M, eds. Neuroimaging in Developmental Clinical Neuroscience. Cambridge, UK: Cambridge University Press, 2009.
[26] Markham JA, Greenough WT. Experience-driven brain plasticity: Beyond the synapse. Neuron Glia Biol 2004;1:351–63.
[27] Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology 2010;35:147–68.
[28] Johnson MH. Functional brain development in humans. Nat Rev Neurosci 2001;2:475–83.
[29] Stevens MC, Pearlson GD, Calhoun VD. Changes in the interaction of resting-state neural networks from adolescence to adulthood. Hum Brain Mapp 2009;30:2356–66.
[30] Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. PLoS Biol 2009;7:e1000157.
[31] Durston S, Davidson MC, Tottenham N, et al. A shift from diffuse to focal cortical activity with development. Dev Sci 2006;9:1–20.
[32] Liston C, McEwen BS, Casey BJ. Psychosocial stress reversibly disrupts prefrontal processing and attentional control. Proc Natl Acad Sci U S A 2009; 106:912–7.
[33] Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A 2004;101:8174–9.
[34] Casey BJ, Trainor RJ, Orendi JL, et al. A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. J Cogn Neurosci 1997;9:835–47.
[35] Rubia K, Halari R, Smith AB, et al. Dissociated functional brain abnormalities of inhibition in boys with pure conduct disorder and in boys with pure attention deficit hyperactivity disorder. Am J Psychiatry 2008;165:889–97.
[36] Stevens MC, Kiehl KA, Pearlson GD, Calhoun VD. Functional neural networks underlying response inhibition in adolescents and adults. Behav Brain Res 2007;181:12–22.
[37] Nesse RM, Berridge KC. Psychoactive drug use in evolutionary perspective. Science 1997;278:63–6.
[38] Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: Possible implications for age differences in substance abuse and other risk-taking behaviors. Brain Cogn 2010;72:114–23.
[39] Tarazi FI, Baldessarini RJ. Comparative postnatal development of dopamine D(1), D(2), and D(4) receptors in rat forebrain. Int J Dev Neurosci 2000;18: 29–37.
[40] Andersen SL. Changes in the second messenger cyclic AMP during development may underlie motoric symptoms in attention deficit/hyperactivity disorder (ADHD). Behav Brain Res 2002;130:197–201.
[41] Galvan A, Hare TA, Parra CE, et al. Earlier development of the accumbens relative to oribitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci 2006;26:6885–92.
[42] Cohen JR, Asarnow RF, Sabb FW, et al. A unique adolescent response to reward prediction errors. Nat Neurosci 2010;13:669–71.
[43] Van Leijenhorst L, Gunther Moor B, Op de Macks ZA, et al. Adolescent risky decision-making: Neurocognitive development of reward and control regions. Neuroimage 2010;51:345–55.
[44] Bjork JM, Knutson B, Fong GW, et al. Incentive-elicited brain activation in adolescents: Similarities and differences from young adults. J Neurosci 2004;24:1793–802.
[45] Galvan A. Adolescent development of the reward system. Front Hum Neurosci 2010;4:6.
[46] Geier CF, Terwilliger R, Teslovich T, et al. Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb Cortex 2010; 20:1613–29.
[47] Schneider S, Peters J, Bromberg U, et al. Risk taking and the adolescent reward system: A potential common link to substance abuse. Am J Psychiatry 2012;169:39–46.
[48] Beck A, Schlagenhauf F, Wüstenberg T, et al. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry 2009;66:734–42.
[49] Steinberg L, Graham S, O'Brien L, et al. Age differences in future orientation and delay discounting. Child Dev 2009;80:28–44.
[50] Cauffman E, Shulman EP, Steinberg L, et al. Age differences in affective decision making as indexed by performance on the Iowa gambling task. Dev Psychol 2010;46:193–207.
[51] Desor JA, Beauchamp GK. Longitudinal changes in sweet preferences in humans. Physiol Behav 1987;39:639–41.
[52] Ernst M, Nelson EE, Jazbec S, et al. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage 2005;25:1279–91.
[53] Bjork JM, Smith AR, Danube CL, Hommer DW. Developmental differences in posterior mesofrontal cortex recruitment by risky rewards. J Neurosci 2007;27:4839–49.
[54] Crone EA, Zanolie K, Van Leijenhorst L, et al. Neural mechanisms supporting flexible performance adjustment during development. Cogn Affect Behav Neurosci 2008;8:165–77.
[55] Gunther Moor B, Crone EA, Van der Molen MW. The heartbrake of social rejection: Heart rate deceleration in response to unexpected peer rejection. Psychol Sci 2010;21:1326–33.
[56] Reyna VF, Farley F. Risk and rationality in adolescent decision making: Implications for theory, practice, and public policy. Psychol Sci Public Interest 2006;7:1–44.
[57] Steinberg L. A social neuroscience perspective on adolescence. Trends Cogn Sci 2008;9:69–74.
[58] Hardin MG, Schroth E, Pine DS, Ernst M. Incentive-related modulation of cognitive control in healthy, anxious, and depressed adolescents: Development and psychopathology related differences. J Child Psychol Psychiatry 2007;48:446–54.
[59] Schramm-Sapyta NL, Morris RW, Kuhn CM. Adolescent rats are protected from the conditioned aversive properties of cocaine and lithium chloride. Pharmacol Biochem Behav 2006;84:344–52.
[60] Torres OV, Tejeda HA, Natividad LA, O'Dell LE. Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. Pharmacol Biochem Behav 2008;90:658–63.
[61] Spear LP, Varlinskaya EI. Low dose effects in psychopharmacology: Ontogenetic considerations. Nonlinearity Biol Toxicol Med 2005;3:97–111.

[62] Millstein SG, Halpern-Felsher BL. Perceptions of risk and vulnerability. J Adolesc Health 2002;31(Suppl 1):10–27.
[63] Monk CS, McClure EB, Nelson EE, et al. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 2003;20:420–8.
[64] Hare TA, Tottenham N, Galvan A, et al. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biol Psychiatry 2008;63:927–34.
[65] Pine DS, Grun J, Zarahn E, et al. Cortical brain regions engaged by masked emotional faces in adolescents and adults: An fMRI study. Emotion 2001;1: 137–47.
[66] Dahl RE. Adolescent brain development: A period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci 2004;1021:1–23.
[67] Figner B, Mackinlay RJ, Wilkening F, Weber EU. Affective and deliberative processes in risky choice: Age differences in risk taking in the Columbia card task. J Exp Psyhol Learn Mem Cogn 2009;35:709–30.
[68] Gardner M, Steinberg L. Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: An experimental study. Dev Psychol 2005;41:625–35.
[69] Gutman DA, Nemeroff CB. Persistent central nervous system effects of an adverse early environment: Clinical and preclinical studies. Physiol Behav 2003;79:471–8.
[70] Hensch TK. Critical period regulation. Annu Rev Neurosci 2004;27:549–79.
[71] Taylor PD, Poston L. Developmental programming of obesity in mammals. Exp Physiol 2007;92:287–98.
[72] Bavelier D, Levi DM, Li RW, et al. Removing brakes on adult brain plasticity: From molecular to behavioral interventions. J Neurosci 2010;30:14964–14971.
[73] Schultz LA, Lore RK. Communal reproductive success in rats (Rattus norvegicus): Effects of group composition and prior social experience. J Comp Psychol 1993;107:216–22.
[74] Gan WB, Kwon E, Feng G, et al. Synaptic dynamism measured over minutes to months: Age-dependent decline in an autonomic ganglion. Nat Neurosci 2003;6:956–60.
[75] Zuo Y, Chang P, Lin A, Gan WB. Development of long-term dendritic spine stability in diverse regions of cerebral cortex. Neuron 2005;46:181–9.
[76] Stevens B, Porta S, Haak LL, et al. Adenosine: A neuron-glial transmitter promoting myelination in the CNS in response to action potentials. Neuron 2002;36:855–68.
[77] Bengtsson SL, Nagy Z, Skare S, et al. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci 2005;8: 1148–50.
[78] McGee AW, Yang Y, Fischer QS, et al. Experience-driven plasticity of visual cortex limited by myelin and nogo receptor. Science 2005;309:2222–6.
[79] He J, Crews FT. Neurogenesis decreases during brain maturation from adolescence to adulthood. Pharmacol Biochem Behav 2007;86:327–33.
[80] Kozorovitskiy Y, Gould E. Adult neurogenesis: A mechanism for brain repair? J Clin Exp Neuropsychol 2003;25:721–32.
[81] Thiriet N, Amar L, Toussay X, et al. Environmental enrichment during adolescence regulates gene expression in the striatum of mice. Brain Res 2008; 1222:31–41.
[82] Kim YP, Kim H, Shin MS, et al. Age-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. Neurosci Lett 2004;355:152–4.
[83] Pfefferbaum B, Wood PB. Self-report study of impulsive and delinquent behavior in college students. J Adolesc Health 1994;15:295–302.
[84] Steinberg L, Cauffman E, Wollard J, et al. Are adolescents less mature than adults?: minors' access to abortion, the juvenile death penalty, and the alleged APA "flip-flop". Am Psychol 2009;74:583-94.
[85] Venkatraman V, Huettel SA, Chuah LY, et al. Sleep deprivation biases the neural mechanisms underlying economic preferences. J Neurosci 2011;31: 3712–8.
[86] Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep 1993;16:258–62.
[87] Irwin CE, Jr., Millstein SG. Correlates and predictors of risk-taking behavior during adolescence. In: Lipsitt LP, Mitnick LL, eds. Self-Regulatory Behavior and Risk Taking: Causes and Consequences. Norwood, NJ: Ablex Publishing Corporation, 1992:3–21.
[88] Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005;62:593–602.