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Adolescent Neurodevelopment

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Abstract

Purpose—The purpose of this paper is to outline notable alterations occurring in the adolescent brain, and 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 towards 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.

Keywords

adolescence; brain; neurodevelopment; brain imaging; cognitive control; reward sensitivity; aversive stimuli; emotions; risk-taking; public policy

Introduction

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, for review). Studies conducted over the last several decades have revealed adolescence to be a time of particularly notable morphological and functional

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transformations in brain that, along with rising 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 paper 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 policy and programs involving adolescents.

Understanding of adolescent brain development continues to escalate rapidly, aided considerably by increasingly informative glimpses of normal, developing human brains provided by continued improvements in imaging technologies. Magnetic resonance imaging (MRI) and other imaging technologies have proved valuable for detailing 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 (see 7 for review). Yet, space and movement constraints limit task-related responses possible within scanners, making it challenging 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 require approaches and levels of analyses largely unavailable with imaging, but more amenable to study using animal models of adolescence. Although the human brain and the behavior it supports is far more complex than that 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 have 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 (e.g., 9; 10; 11), increases in novelty-seeking, sensation-seeking and risk-taking (12; 13; 14; 15), and greater per occasion alcohol use (e.g., 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 (see 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 is 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 close to 50% of the synaptic connections in some regions, but with little decline in others (21). This 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 further later. 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 utilization 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 (see 1, for review). There are also

major shifts in the speed and timing of information flow across the brain that influences functional connectivity across brain regions during adolescence (24). Speed and efficiency of information flow across relatively distant regions is accelerated during adolescence as neuronal axons interconnecting certain brain areas become insulated with a white-colored, fat-enriched substance called myelin, thereby markedly increasing the speed of electrical transmission along axons, while 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 their 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 – i.e., 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 prior to 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 non-cortical areas is also thought to contribute to adolescent-characteristic behaviors. Subcortical regions receiving notable attention that will be reviewed below include areas modulating social, aversive and emotional stimuli such as the amygdala, and regions implicated in the processing of rewarding stimuli, as exemplified below 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 that 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.

Yet, development of the brain is not simply a chronology of developmental immaturities, with different areas coming on-line at different times. Rather, contemporary views of brain maturation consider it to be a dynamic process by which different 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 later presumably aided by the preferential myelination of longer axonal tracts as discussed earlier. 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 (see 7 for

review). 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), while at the same time increasing activity in subcortical regions modulating emotional reactivity such as the amygdala, as discussed later.

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 strengthening 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.

Dopamine, the ventral striatum and adolescent-related alterations in reward sensitivity—Novel stimuli, exciting and risky situations, as well as 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 2-7 fold 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 the one hand, adolescents sometimes (41; 42; 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). At first blush, these data might seem counter to the avidity with which adolescents pursue rewards, Yet, attenuated activations of ventral striatum during reward anticipation is associated with greater risk-taking biases among adolescents (47) and with elevated levels of impulsivity among alcoholics but not a comparable 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 that may perhaps serve 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 rise to peak in mid-adolescence (i.e., about 14-15 years) and then to gradually decline into adulthood (49; 50; 51). 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) (52). Data supporting a strong biological component to this enhanced reward responsivity have been obtained using simple animal models, with adolescent rats likewise often more sensitive than adults to the rewarding properties of stimuli that range from desirable tastes, social peers, and novelty, to drugs of abuse including cocaine, amphetamine, nicotine, and alcohol (for review, see 38).

The 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 (53). For instance, the amygdala of adolescents is activated less than that of adults in response to aversive outcomes (reward omission) (53). 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 high penalty in adolescents, data suggesting that this area is less sensitive to penalties in adolescents than adults (54). These data are consistent with other emerging evidence that neural responses to negative feedback may mature later than responses to positive feedback (55; 56).

A reduced responsiveness to aversive stimuli during adolescence is often (50; 57; 58) although not always (59) evident behaviorally. For instance, sensitivity to negative feedback in a gambling task was found to be low during early-mid adolescence, and to increase gradually thereafter (50; 58). 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 non-drug 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; 60; 61). 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 (62). 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 (63).

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 amygdala to emotional (often fearful) faces relative to neutral faces. In some (e.g., 64; 65) but not all (e.g., 66) studies, adolescents were found to exhibit greater amygdala activation to emotional faces than adults (and children, when studied), 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 (65). Indeed, although the rational decision making of adolescents reaches adult-typical levels by mid-adolescence, this capacity can be reduced under stressful, emotionally charged and arousing circumstances (49) – a phenomenon called “hot cognitions” (see 67). For instance,

when both emotional and non-emotional versions of a risk-taking task were examined, adolescents exhibited more risk-taking than adults only under the emotional version of the task (68). 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, but not when individuals at both ages were tested alone (69). Adolescent engagement in risky behaviors commonly occurs in social situations (58).

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 still being sufficiently malleable to adapt to new experiences throughout life. The balance between plasticity and stability is tilted towards 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 (70; 71; 72). At maturity, the balance is shifted toward greater stability of neural circuits, although the capacity for plasticity is still present in restricted form (73). 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. Rises 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 (74).

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 formed and others eliminated at notably greater rates than seen in the mature brain (75; 76). Some of the synaptic pruning that is seen during adolescence appears in part experience-dependent (76), as does the process of myelination, with axonal myelination driven partly by the amount of electrical activity passing along to-be-myelinated axons (77). Findings consistent with experience-dependent myelination are beginning to emerge from human imaging work as well. For instance, in a study of professional musicians, the amount of white matter development in performance-relevant tract pathways was correlated with amount of time spent practicing, especially practice time during childhood and during early/mid-adolescence (78). 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 (79).

Basic science studies have also revealed evidence for 4-5 times higher rates of formation of new neurons during adolescence than in adulthood (80). 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 (e.g., 81). Such beneficial effects have been seen following exposures during adolescence (82) and in adulthood (83), 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 plasticity might extend into adulthood. Yet, 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, as illustrated below.

(a) Adolescents often seem to view rewarding and aversive stimuli differently than do adults, 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 pursuit of, continued engagement in, and the escalation of risky and exciting activities, particularly when prior activities proved rewarding but without disastrous consequences. Indeed, risk-taking has been viewed as “one dimension of the drive for thrills and excitement” (84, p.296). Attenuated aversive consequences in the face of a potential for greater rewarding 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 as well as age restrictions to limit access to cigarettes, alcohol, gambling, and so on; restricting availability of high caloric/low nutritional capacity food and drinks in schools). On the other hand, 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 (57).

(b) 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 regions of the frontal cortical 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 vs. for culpability to illegal acts occurring under conditions favoring “hot” cognitions (e.g.,49). 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 showing that sleep deprivation likewise shifts brain

activation toward “hot cognitions” (85), taken together with evidence for a partially biologically-driven phase shift towards 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.

(c) 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 (87) and perhaps even rational under some circumstances (57). 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 (58), 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 risk 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 adolescent neurobehavioral function is influenced by genetic background and prior experiences. Many youth traverse adolescence relatively easily, with their risk-taking limited and without notable adverse consequences (sometimes perhaps more by happenstance than design). Yet, for other individuals, adolescent behavioral choices have severe consequences, including lasting alcohol/drug abuse, incarceration, or even death (with mortality rates increasing 2-4 fold during the otherwise healthy adolescent period (88). For some adolescents, adjustment problems may evolve into psychological disorders, with rises in the incidence of a variety of disorders during adolescence (89). Little is known of how development of the adolescent brain influences expression of individual differences across the course of adolescence, nor of the role of environmental experiences in the emergence of resiliencies and vulnerabilities among individual adolescents. More knowledge of individual variation in such resiliences/vulnerabilities (and how to detect these using behavioral- or bio-markers) are 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. While 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:

~To what degree do adolescent experiences (including those provided by adolescent risk-taking) customize the maturing brain in ways commensurate with those experiences?

~What experiences are effective, how much experience is necessary, and to what degree are these experience-dependent adaptations beneficial or detrimental?

~How long-lasting are these effects?

~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?

~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 off-track during adolescence may yield substantially more benefit than waiting until those trajectories have diverged considerably later in life.

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