The Transitional Age Brain

"The Best of Times and the Worst of Times"

Winston W. Chung, MD[a], James J. Hudziak, MD[b,*]

KEYWORDS

• Transitional age youth • Brain development • Transitional age brain • Behavior • Neuroscience

KEY POINTS

- Over the past 2 decades, there have been substantial developments in the understanding of brain development.
- Progress in neuroimaging has allowed us to better understand the nuances of the development of cortical, subcortical, and white matter structures.
- Modern neuroscience, genomics, and epigenomic studies allow us a lens through which to develop an understanding of transitional age youth (TAY) behavior from a neurodevelopmental perspective.
- Developing brain building health promotion and illness prevention approaches for TAY will likely yield reductions in morbidity and mortality, enhance individual life trajectories, and have a life-long impact.

INTRODUCTION

A great deal of attention has been paid to the so-called zero to 3 period of brain development. Although clearly an important focus of neuroscience and public health, there is emerging evidence that a second critical period of neurodevelopment exists, bracketed by the onset of the peripubertal process to the completion of cortical organization (roughly ages 13–25). This 'transitional age brain' (TAB) epoch is marked by an increase in risk for morbidity, mortality, drug and alcohol use/misuse, and the onset of persistent psychiatric and nonpsychiatric medical conditions.

The central hypothesis is that the TAB has fully matured risk-taking hardware because of early maturation of subcortical brain regions (amygdala, nucleus

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[a] Vermont Center for Children, Youth, and Family, University of Vermont Medical Center, 1 South Prospect Street, Arnold 3, Burlington, Vermont 05401, USA; [b] University of Vermont College of Medicine and Medical Center, 1 South Prospect Street, Arnold 3, Burlington, Vermont 05401, USA

* Corresponding author.

E-mail address: James.Huziak@med.uvm.edu

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accumbens, etc) but does not yet have matured regulatory hardware (fully pruned prefrontal and related cortical regions). We maintain that adolescents (13–17 of age) and their TABs benefit from imposed external regulatory systems in the form of parents, family members, teachers, and coaches. Even with external control and expectations, transitional age youth (TAY) remain at very high risk for morbidity and mortality associated with suicide, substance use and misuse, psychiatric illness, and accidents. At the same time that TAY and their maturing brains need more external regulatory support and lower risk environments, they instead have easier access to alcohol and drugs, high-risk social activities, and loss of close parenting and supervision. In other words, these negative environmental factors are in play at a very vulnerable time of brain development, in which the regulatory regions of the brain are undergoing the critical process of maturation.

Herein, we discuss the neurodevelopmental processes (with a special emphasis on pruning) that place TAY at high risk to make impulsive, poorly regulated decisions. We present a description of the symphony of brain development (neurogenesis, synaptogenesis, myelination, and pruning) from fertilization to the end of the TAB period to set the stage for just why the TAB epoch is a critical period. Although we emphasize the potential negative consequences of the TAB epoch, we also want to acknowledge that the same features of adolescent and young adult brain development may be a strength that allows TAY and TAB to respond to psychosocial interventions or to changes in environmental context with improved trajectories into adulthood.

EARLY BRAIN DEVELOPMENT

With advances in both structural (MRI) and functional (fMRI) imaging techniques, along with creative experimental designs using fMRI, information about the development of the human brain has been rapidly expanding. Still, research in the field continues to rely on studies the using other mammalian species with the extrapolation of data to humans.[1]

Human brain development begins during the third week of gestation and continues to about the middle of the second decade, when the components involved in executive function become fully formed. It is a process that is intricate and tightly controlled, yet allows for some flexibility to adapt to the idiosyncrasies of the environment. One theme that emerges is that the brain matures by becoming more interconnected and each region becoming more specialized. Another theme that emerges is the process of overproduction before the elimination of excessive cells and connections based on experience, ultimately resulting in an efficient and unique processor.

The process begins with gastrulation, with differentiation of neural progenitor cells, followed by formation of the neural tube, then the neocortex and synaptic pathways. Around gestational week 28, the number of neurons in the human brain is at its peak, a level 40% greater than in adults. Dendritic growth, arborization, and synaptogenesis begin to accelerate rapidly.[2–9] The rate of synaptogenesis reaches its peak around gestational week 34, but the net decrease of synapses does not begin to decrease until the onset of puberty.[2,7–10] At the same time, up to 50% of the neurons undergo cell death to begin the process of establishing definitive connections.[11]

After birth, neurogenesis is largely complete, and a dynamic process of synaptogenesis, myelination, programmed cell death, and pruning ensues as intrinsic and extrinsic signals interact. In the initial critical period up to age 3, development is dominated by synaptogenesis and by age 2 to 3, a toddler has more synapses than an adult and peaks at a level nearly twice that of adults.[12,13] Some networks connections are

exuberant, and entire networks are sometimes formed that are not found in adults.[14–16] This process is regulated by neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which blocks apoptosis.[17,18]

Gray and white matter develop in concert with sensorimotor areas developing first, and then progressing to spatial orientation and language, before concluding with association regions (frontal lobe). There is a profound temporal mismatch between early subcortical development (limbic areas including the nucleus accumbens, amygdala, and others) and cortical regulatory regions. This period of cortical organization or pruning takes place during this second critical period during the transitional age (13–25 years), when the final pruning and myelination takes place. This leads to improved executive function such as attention, concentration, impulse control, reasoning, planning, problem solving, and mood regulation.

BRAIN PATTERNING AND PLASTICITY

During the prenatal period, a basic structure of brain organization is developed. The core structures from the spinal cord to the neocortex and the major compartments within these structures are formed, and there is an initial partitioning of the neocortex into well-defined functional areas.[19–23] This initial patterning is underdefined, malleable, and based largely on intrinsic signaling.[24] Beginning in the late prenatal period, brain development is exquisitely responsive to extrinsic signaling or experience. Significant alterations to the brain structure can occur depending on whether the environment is enriched or deprived. This plasticity allows the mammalian brain to adapt to its environment.

The early patterning of the brain is well illustrated through the development of the neocortex. Emx2 and Pax6 are 2 signaling molecules produced in opposite gradients along the anterior–posterior axis in the neocortical proliferative zone.[25] The concentration of Pax6 is greatest in the anterior and lateral regions, whereas the highest concentration of Emx2 is in the posterior and medial regions. It is the relative concentration of each of these signaling molecules that contribute to the early patterning.[19,25,26] High concentration of Pax6 and low concentration of Emx2 leads to the development of motor cortex (M1). However, a low concentration of Pax6 and a high concentration of Emx2 toward the caudal end lead to the development of the visual cortex (v1). The somatosensory cortex emerges in between, where the concentrations of Pax6 and Emx2 are intermediate; knockout mouse models of Pax6 and Emx2 confirm that it is indeed the concentration of 1 signaling molecule in conjunction with the other that produces the specific patterning. When Pax6 expression is blocked, visual areas enlarge and somatosensory and motor areas shrink. When Emx2 expression is blocked, the opposite is true.

Despite this early patterning, the structure and function of these areas remain highly malleable and subject to experience. Greenough and coworkers have coined the term “experience expectant processes” to explain the phenomenon of synaptic and neuronal exuberance and subsequent pruning. This process allows for adaptation to ubiquitous environmental conditions that are common to all species.[27] However, it also suggests that the environment is a necessary condition for the normal development of certain neurobehavioral functions. An example of this would be the seminal study conducted by Hubel and Weisel on the early postnatal development of the visual cortex.[28,29] By limiting the visual input of 1 eye on a primate, the bands of the active eye in the ocular dominance column expanded into the area of the deprived eye. Similarly, in Bachevalier and Mishkin’s study, infant monkeys who sustained early lesions to the inferior temporal cortex were able to regain most of their function

with only minimal deficits compared with adults who were not able to regain their function.[30] It is also noteworthy that infant monkeys that sustained medial temporal lobe lesions were not able to regain their function, suggesting that neural plasticity also has its limits.

Studies of human brain development also highlight the importance of experience and the environment. For example, poverty has been shown to be associated with significant impacts on brain development. Hanson and colleagues[31] have shown lower total gray matter volumes, frontal and parietal volumes, and decreased total gray matter trajectory in children from lower income families. Additionally, early life stressors, which include low socioeconomic status, but also neglect and abuse, led to smaller amygdala and hippocampal volumes.[32] Decreases in cortical gray matter thickness, right hemispheric volume, and left and right anterior insula volume[33,34] are associated with early childhood depression. Interestingly, a variation of parent–child interaction therapy developed by Luby and associates,[35] named parent–child interaction therapy—emotion development, seems to be helpful for early childhood depression. Connectivity among regions important for emotional regulation is also similarly affected. Increased early life stressors was associated with decreased and atypical connectivity between the amygdala and the prefrontal cortex.[36–39] And, Luby reported that lower income-to-need ratio was associated with reduced negative connectivity between left hippocampus and amygdala and the right superior frontal gyrus in addition to connectivity of both the amygdala and hippocampus bilaterally.[40]

Although depravation can lead to thinning, atypicality, and loss of function, an enriched environment can have the opposite effect. Early on, Hebb noted rats reared in a "home" environment outperformed rats reared in a laboratory environment.[41] Later, Rosenzweig and his colleagues also noted difference in brain weight, and other physical and histologic differences between rats reared in enriched versus impoverished environments.[42–50] More recently, Greenough and coworkers showed that rats reared in a complex environment (large groups and objects in a cage that was frequently cleaned) had 20% to 25% more dendrites per neuron, and in those animals that were fitted with a monocular occluders, the exuberance was noted only unilaterally.[51–55] Moreover, the glial cells were also affected, with greater numbers and complexity, as well as an enhanced capillary system.[51,56] Similar effects have been observed in adult rats reared in complex environments.[57,58] In human studies, practice of specific skills such as juggling or playing a musical instrument has led to structural and white matter changes.[59–69]

GRAY AND WHITE MATTER MATURATION

Early MRI morphometry studies compared children and adults. In Jernigan and Tallal's seminal study, gray matter volumes were shown to be considerably larger in school-aged children than in young adults.[70,71] And in Giedd's landmark study, he showed that the volume of the cortical gray matter follow an inverted U shape, with peaks in late childhood and a surge just before puberty and occurring about 1 to 2 years earlier in girls.[72,73] In subsequent studies, Shaw and Raznahan have also reported a curvilinear growth pattern of cortical thickness, a component underlying cortical volume along with cortical surface area.[74,75] However, other studies have not identified the "inverted U" shape but rather monotonic linear decreases in cortical thickness. Sowell, Muftuler, Koolschijn, Mutlu, and Ducharme and their colleagues all primarily found first-order linear declines with the youngest children in this study being around 5 years old.[76–80] More important, Ducharme and associates[78] found postprocessing quality control procedures significantly impacted the complexity of the growth trajectories.

When no quality control procedures were implemented, there were more areas with quadratic and cubic trajectories. The biological underpinnings of the volumetric and cortical thickness changes are owing to arborization as well as continued glial cell maturation opposed by pruning of neuronal processes.[11] Changes in neuronal size, glial cell density, and vasculature could also contribute to cortical thickness changes.[81]

More recent structural MRIs allowed for more precise measurements of cortical thickness.[82,83] These more detailed studies were able to show a modal pattern of cortical development, suggesting regional specificity in cortical thickness.[81] Gogtay and coworkers[84] reported that phylogenetically older regions matured (thinned) earlier than newer regions. They also observed that the maturation process starts with lower order somatosensory and visual cortices before proceeding to multimodal and supramodal cortices.[84] The lateral prefrontal cortex and the temporal poles, regions processing motivation, goal-setting, and integration of emotion, are the last regions to mature.[84–87] The maturation of various cortical regions has been correlated with performance measures. Maturation of the prefrontal cortex is related to cognitive intelligence, the anterior cingulate cortex is related to impulse control, the motor cortex is related to fine motor skills, and the left hemisphere area is related to increased language processing skills.[88–91] Our group has shown that, in typically developing children followed across development, it is possible to relate specific cortical thickness regions in whole brain analyses that correlate with quantitatively different expressions of common traits such as aggression, anxiety, attention, emotional regulation, and externalizing problems.[92–96]

The subcortical gray matter also undergoes significant changes, although to a lesser degree compared with the neocortex.[79,97–100] The caudate, which has traditionally been implicated in control of movement and muscle tone, and more recently in mediating higher order cognitive functions, had previously been shown in some but not all studies to also have a curvilinear developmental trajectory with peaks during the preadolescent to adolescent years.[101,102] However, in a more recent study, Ostby and associates[100] analyzed multiple structures in the basal ganglia (caudate, putamen, and pallidum), and nucleus accumbens, and found a linear decrease over time. The hippocampus and the amygdala on the other hand, showed an increase in size with age.[97–99,103,104]

Unlike gray matter, white matter volume begins to increase in the postnatal period and continues into middle adulthood.[105–107] The development of diffusion tensor imaging has allowed the visualization of white matter by measuring proton diffusivity. As fiber tracts mature and myelination proceeds, diffusion or fractional anisotropy increases.[108] Although many studies found that white matter volume linearly increases over time, some studies have suggested it may have a curvilinear inverted U function, reaching its peak during the second decade.[71,72,109,110] Also like gray matter, different tracts mature at different times. Tracts such as the corticospinal tract and corona radiata are mature by adolescence, but tracts responsible for executive function and emotional and behavioral control such as the internal capsule are still maturing in the adolescent. The continued maturation of these tracts likely is a major contributor to the improvements in modulation of adolescent behavior.[111–113] The maturation of the white matter tracts has implications for other cognitive functions, such as intelligence, visuospatial skills, response inhibition, memory, reading skills, and language.[114]

The nuances in the development of various cortical and subcortical regions are noteworthy, but further investigations with a longitudinal design are needed to confirm the results.

TRANSITIONAL AGE BRAIN MISMATCH HYPOTHESIS

In almost every measurable domain, adolescence is a developmental period of strength and resilience. Compared with young children, adolescents are stronger, bigger, and faster, and are achieving maturational improvements in reaction time, reasoning abilities, immune function, and capacity to withstand cold, heat, injury, and physical stress. Yet, despite these robust maturational improvements in many domains, overall morbidity and mortality rates increase by 200% over the same interval of time.[115] This doubling in rates of death and disability from the period of early school age into late adolescence/early adulthood is likely owing to difficulties in the control of behavior and emotion. This period is, therefore, marked for the high rates of accident suicide, violence, and health problems related to risky sexual behaviors.[115] In addition, adolescence is the peak time of emergence for several types of mental illnesses, including anxiety disorders, bipolar disorder, depression, eating disorders, psychosis, and substance abuse. In the National Comorbidity Survey Replication Study, Kessler and colleagues[116] found that 50% of most mental illnesses people experience emerge by age 14 and 75% start by age 24.

A simplistic explanation of the developmental mismatch can be understood through the emerging understanding of the development of 3 key regions of the brain: the nucleus accumbens, amygdala, and prefrontal cortices.

The nucleus accumbens is the home of motivation, passion and pleasure. Afferents from the ventral tegmental area, specifically the A9 and A10 nuclei travel over the mesolimbic dopamine pathway to stimulate the nucleus accumbens via dopaminergic neurons. Activity in the nucleus accumbens influences how much effort an individual will expend in pleasure and reward-seeking behavior. A developing nucleus accumbens is believed to contribute to the often observed tendency that some TAY prefer activities that require low effort yet produce high excitement. When mature, the mesolimbic dopaminergic pathway terminates in prefrontal and frontal cortical regions and is responsible for attentional control, concentration, and mood regulation. However, those frontal regions are not yet organized and the mismatch of drive without control is the essence of the TAB and central to the developmental mismatch theory.

The amygdala plays a key role in both emotional recognition and regulation. It increases in volume from late childhood until late adolescence, with a decelerating rate of growth after the age 16.[117] Pathways into and out of the amygdala are responsible for integrating emotional reactions to both pleasurable and aversive experiences. It is hypothesized that, during the developmental mismatch epoch, the amygdala contributes to 2 behavioral effects: the tendency for adolescents to react to situations with "hot" emotions rather than more controlled and "cool" emotions and the propensity for youth to misread neutral or inquisitive facial expressions from other individuals as a sign of anger.[74] As the TAB matures, the functional connectivity of the amygdala changes dramatically and amygdala activity becomes more closely linked to activity in those prefrontal cortex regions involved in emotional regulation. This signals an end to the TAB period and the beginning of a more neurologically regulated period referred to as adulthood.[118]

Last, the prefrontal cortex is the key area of the brain involved in attention, emotional regulation, impulse control, cognitive flexibility, planning, and judgment. To do this, it processes complex information, requiring inputs from many brain regions. It allows a person to make decisions and select a course of action based on impulse inhibition, foreseeable consequences, and personal goals. It also happens to develop much later than the nucleus accumbens or the amygdala because cortical thinning or gray matter volume loss (maturation) occurs from the back of the brain to the front. In fact, the

prefrontal cortex is the last brain region to complete development. As a consequence, TAY rely much more on the emotional regions of their brain, such as the amygdala and other limbic regions, to guide their behavior compared with adults.[74,119] In other words, TAY do not yet have the brain structures in place that allow the consistent use of the prefrontal cortex for its primary responsibilities of planning, judgment, cognitive flexibility, and impulse control. This mismatch in maturational timing is most exaggerated during the adolescent period, when the subcortical structures including the hormone fueled limbic system is already developed while the prefrontal cortex and the white matter tracts connecting to the prefrontal cortex continue to mature.[120] Most recent studies seem to bear this out, indicating that risk-taking behaviors, sensation seeking, and heightened emotional reactivity are linked to the developmental mismatch in maturation of cortical and subcortical structures.[121] The fact that puberty seems to be starting earlier means that the "mismatch years" are being extended.

As a result of this mismatch, TAY at times use poor judgment and take excessive risks. The relative delay in the maturation of frontal cortical areas as well as those networks connecting to them leaves adolescents vulnerable to performance impairments of higher order cognitive functions, such as cognitive control and response inhibition when stressed.[122–125] TAY have increased activation of the ventral striatum to rewards and decreased activation during reward anticipation, which leaves them vulnerable to risk taking.[126–130] Further, their amygdala are less activated in response to aversive outcomes while exhibiting social emotional bias, resulting in more risky behavior in the presence of others.[131–135] As such, they more frequently make poor decisions and take excessive risk.[84]

Similarly, the protracted development of the uncinated fasciculus provides insight into the difficulty TAY have in emotional regulation. The uncinated fasiculus is a fiber pathway composed of frontotemporal connections that include projections from orbitofrontal cortex to the anterior temporal cortex, as well as the amygdala.[136,137] It has been shown to display age-related increases in microstructural integrity well into adulthood.[138] Although the amygdala has been implicated in mediating negative affective states such as fear and anxiety, hemodynamic activity within aspects of the orbitofrontal cortex has been associated with emotion regulatory processes.[139] The continued development of the orbitofrontal cortex and this pathway that links it to the amygdala is what allows for improved affective regulation as TAY grow into adulthood.

EMOTION REGULATION AND THE BRAIN

The neuropsychological processes important for emotion perception, allowing the generation of contextually appropriate, complex affective states, emotional experiences (feelings), and behaviors, include the identification of the emotional significance of an environmental stimulus, the production of an affective state and emotional behavior, and the regulation of the affective state and emotional behavior. Findings of neuroimaging studies indicate that specific neural regions may be important for more than one of these processes. The processes may be depend on the functioning of 2 main neural systems: a ventral system and a dorsal system. The ventral system, including the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex, is important for the identification of the emotional significance of environmental stimuli and the production of affective states. It is additionally important for automatic regulation and mediation of autonomic responses to emotive stimuli and contexts accompanying the production of affective

states. The dorsal system, including the hippocampus and dorsal regions of the anterior cingulate gyrus and prefrontal cortex, regions where cognitive processes are integrated, is important for the performance of executive functions, including selective attention, planning, and effortful rather than automatic regulation of affective states.[140]

The emotional circuitry of the brain is being shaped continuously by experiences that impinge on the nervous system during prenatal development and throughout life. This experience-induced plasticity has been documented in the brain in a variety of animal models and there is now substantial evidence on the effect of stressful and stimulating environments on the developing human brain and associated behavior. Most evidence is obtained by structural MRI studies of children that experienced adversity. Abused children are shown to have smaller orbitofrontal volumes and, the smaller the orbitofrontal volume in the abused sample, the more severe the social stress was reported.[141] In another study, higher parental ratings of internalizing behavior and anxiety were correlated with a larger amygdala volume. Furthermore, children continuously exposed to maternal depressive symptoms from birth had significantly larger left and right amygdala than children with no such exposure.[142] Such a developmental pattern in the amygdala has been suggested to occur in the autistic brain.[143,144] Research suggests that some of these alterations in brain structure are caused by epigenetic regulations. For example, child abuse is associated with alterations in the epigenetic regulation of the glucocorticoid receptor extracted from the hippocampus of suicide victims with a history of child abuse compared with those with no abuse history along with controls. In the hippocampus, decreased levels of glucocorticoid receptor messenger RNA were observed.[145] Several pathologic conditions (eg, major depression, posttraumatic stress disorder) are associated with decreased density or volume of the hippocampus.[146,147]

EPIGENETICS, GENE EXPRESSION, AND A PERIOD OF VULNERABILITY AND OPPORTUNITY

As discussed, epigenetic regulations can have powerful effects on the brain. The main factors that contribute to epigenetic changes in the adolescent brain are DNA methylation, histone modification, and microRNAs or noncoding RNAs. DNA methylation is generally associated with gene silencing as a methyl group binds to CpG islands blocking RNA polymerase, although recent evidence suggests that the effects of methylation could be more complicated.[148–150] Histone modifications alter the accessibility of the transcription machinery to the DNA and include methylation, acetylation phosphorylation, and ubiquitination.[151] And last, microRNAs are small noncoding RNAs that regulate posttranscriptional gene expression by affecting the translational efficiency of specific messenger RNA targets.[152–154] Noncoding RNAs regulate many levels of transcriptional process such as modulating chromatin structure by recruiting coregulators to the transcriptional unit.[153,154]

During normal mammalian brain development, adolescence seems to be a time of great epigenetic shift. Somel and associates[155] showed that there was heightened level of epigenetic modulation during adolescence, which the authors believed extended neuronal plasticity. Similarly, Lister and colleagues[156] also identified large-scale reconfiguration of the epigenome during periods of heightened synaptogenesis such as during adolescence. These changes in the epigenome likely help to regulate sex differences in the brain. The preoptic area is an area important for sexual, parenting, and thermoregulating behaviors. In this area, the expression of the ERα is modulated by estradiol resulting in 30% greater methylation in females compared with males.[149] In males, higher levels of histone deacetylases play a key role in

programming male sexual behavior.[157] And last, Zinc Fingers, which represses transcription by binding to regulatory regions of DNA, plays a role in modulating pubertal onset in both males and females.[158,159]

With the elevated level of epigenetic modulation and increased brain flexibility, adolescents are at increased risk of detriment and long-term impairment. In fact, studies were able to show the differential effects of substances on the adolescent brain compared with the adult brain. With repeated exposure to ethanol, adolescent rats showed reduced expression of dopamine receptor D_2, and glutamate ionotropic receptor NMDA type subunit 2 in the prefrontal cortex and altered acetylation levels of histones H3 and H4, which was mediated by elevated histone acetyltransferase (histone deacetylase), in the frontal cortex, striatum, and nucleus accumbens.[160] The same exposure to adult rats showed no changes in the measures as listed. Other studies have shown similar long-term changes to the organization of the reward and emotional circuitry.[161–164] Nicotine studies showed the greatest gene alterations occurred during the mid-to-late adolescent periods, corresponding with the age of greatest dependence.[165] Similarly, psychostimulant studies showed more pronounced effects in the adolescents compared with adults. Amphetamine and methylphenidate both showed decreased messenger RNA levels of BDNF in the prefrontal cortex and hippocampus but actually increased BDNF levels in adult prefrontal cortex.[166] The attenuation of a factor involved in neuronal growth and plasticity in adolescents is certainly concerning.

But, just as the heightened brain plasticity could result in detrimental effects, an enriched environment could produce benefits. A single week of voluntary exercise in adolescent rats led to significant increases in BDNF, and epigenetic regulators such as histone deacetylase and DNA methyltransferase decreased.[167] With 4 weeks of exercise, the adolescent rats demonstrated improved memory that was sustained into adulthood.[168] Adults who exercised showed immediate benefits in memory enhancement and elevation of BDNF but no long-term benefits. Interestingly, low-to-moderate intensity exercise was sufficient for increased neurogenesis and increased level of BDNF, whereas high-intensity exercise may have triggered a stress response that offset the benefits of exercise.[169] Even more impressive, social enrichment was able to mitigate impact of prenatal alcohol exposure in a rat model of fetal alcohol spectrum disorder.[170]

Evolutionarily speaking, adolescence is a time of transition where independent skills are acquired to facilitate the transition into adulthood. Brain plasticity provides opportunity for the developmental changes in TAY, creating a physiologic environment that intersects with the environmental and emotional changes that contribute to independent skill development. Increases in peer-directed social interactions, and intensification of risk taking and novelty seeking behaviors mediated by increases in dopamine levels and enervation may contribute to more successful mating and independence.[1,171,172] To balance this increase in risk, the increased emotional reactivity may contribute to heightened vigilance of risks and threats thereby increasing opportunity for survival.[122] Increased epigenetic modulation and brain plasticity may contribute during this time of great change by mediating learning of new information. It was possibly a survival advantage at some point in human evolution, especially when one considers the differences in life expectancy and social pace across the history of human development. However, given the statistics on morbidity and mortality, it is important to consider both the advantages and the potential risks that result from this mismatch in modern TAY. The question as to whether this elevated plasticity is a unique adolescent risk factor or a transition to a more stable brain remains.[173]

SUMMARY

Over the past 2 decades, there have been substantial developments in the understanding of brain development. Progress in neuroimaging has allowed us to better understand the nuances of the development of cortical, subcortical, and white matter structures. Modern neuroscience, genomics, and epigenomic studies allow us a lens through which to develop an understanding of TAY behavior from a neurodevelopmental perspective. We now understand, to a greater degree, why adolescents have difficulty with impulse control, risky behavior, and are disproportionately influenced by their peers. Although our current science has not provided us with all the answers, we can now state confidently that negative environmental influences impact the structure and function of the human brain and the thoughts, actions, and behaviors that result. Armed with emerging evidence that positive environmental influences can influence positively the structure and function of the brain and foment improved academic, memory, mood, and emotional regulatory outcomes,[174] it is now time for child and adolescent psychiatry to design brain-building health promotion and illness prevention approaches for all children, but particularly those in the TAB risk epoch. Developing brain-building health promotion and illness prevention approaches for TAB individuals will likely yield reductions in morbidity and mortality in this high-risk period, enhance individual life trajectories, and possibly have life-long impact on friends and families of TAY.

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