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Current Perspective

Developmental trajectories of brain maturation and behavior: Relevance to major mental illnesses

Sedona Lockhart, Akira Sawa, Minae Niwa*

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287, USA

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ABSTRACT

Adverse events in childhood and adolescence, such as social neglect or drug abuse, are known to lead to behavioral changes in young adulthood. This is particularly true for the subset of people who are intrinsically more vulnerable to stressful conditions. Yet the underlying mechanisms for such developmental trajectory from early life insult to aberrant adult behavior remains elusive. Adolescence is a period of dynamic physiological, psychological, and behavioral changes, encompassing a distinct neurodevelopmental stage called the 'critical period'. During adolescence, the brain is uniquely susceptible to stress. Stress mediators may lead to disturbances to biological processes that can cause permanent alterations in the adult stage, even as severe as the onset of mental illness when paired with genetic risk and environmental factors. Understanding the molecular factors governing the critical period and how stress can disturb the maturation processes will allow for better treatment and prevention of late adolescent/young adult onset psychiatric disorders.

1. Introduction

In the past, many scientists have addressed the question of how early life events may contribute to the shaping of adult behavior. These investigators include psychologists like Erikson and Piaget who stated that during the long-term trajectory there are several specific stages that contribute to the proper development towards adult behavior. For example, Erikson's theory of psychosocial development suggests there are eight stages of psychosocial conflicts in ego growth from infancy to adulthood.[1] Piaget's four stages of cognitive development takes into consideration how biological maturation and environmental factors facilitate cognitive development throughout the lifespan.[1]

Consistent with such a conceptual framework of psychological development, recent clinical and epidemiological evidence has indicated that any early life disturbances, such as abuse or neglect, may lead to aberrant behaviors in adulthood, and potentially enhance the risk for a wide range of psychiatric conditions.[2–6] For example, aberrant use of drugs, such as marijuana, in adolescence has been correlated to a heightened risk of psychosis.[7]

In rodent models, early life stress also reportedly impairs mood, cognition, memory, and learning in adulthood.[3,5] Many of these studies have found that early stress elicits several molecular and structural changes in the brain, which accompany the behavioral deficits in adulthood.[8] Thus, rodent models may be useful in studying mechanisms of how adverse events in early life may underlie adult behavior during the developmental trajectory.

Major psychiatric conditions, such as schizophrenia or severe cases of bipolar disorder, emerge in late adolescence and young adulthood, and most display a chronic deteriorating course after onset. Thus, there are two major mechanistic questions: the first being why these disorders often emerge after puberty, although the initial risk events may occur years earlier, sometimes even during prenatal stages; and the second being why the emerged deficits frequently become sustained throughout adulthood.

2. Dynamic changes in the adolescent brain

During adolescence, the brain, including the cerebral cortex, changes and matures drastically (Fig. 1). For example, in the first half of adolescence, massive elimination of synapses occurs, specifically among glutamatergic neurons.[9] This event occurs not only

* Corresponding author.
E-mail address: mniwa1@jhmi.edu (M. Niwa).
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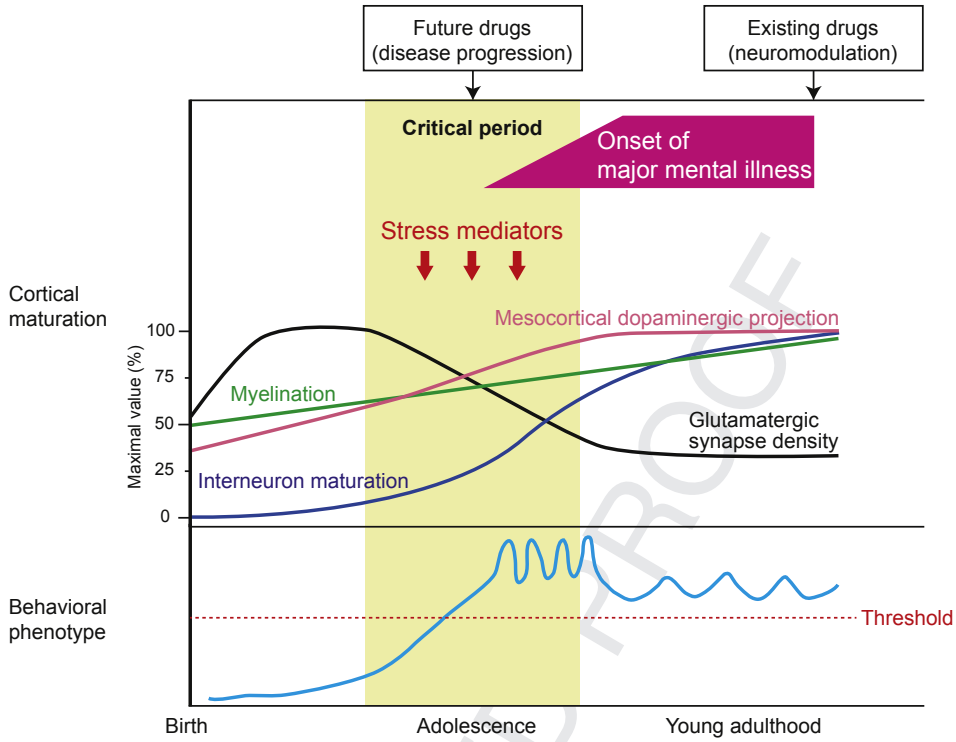

Fig. 1. Psychological cortical maturation and behavioral patterns in developmental trajectory of major mental illnesses. The upper panel shows the developmental trajectory of brain maturation. Brain maturation, including maturation of interneurons and dopaminergic projections, pruning of glutamatergic synapses, and increased myelination, occurs from birth to young adulthood, most dynamically during adolescence. Stress mediators regulated by genetic and environmental factors affect this maturation processes during this critical period. Aberrant brain maturation induced by stress mediators might be an essential mechanism underlying the disease. The lower paner shows the course of abnormal behavioral patterns related to major mental illnesses. Disturbance of brain maturation caused by stress mediators during the critical period may increase vulnerability to major mental illnesses, for which the devastating behavioral phenotype (over the threshold) will begin to emerge in late adolescence and early adulthood. Adapted from Jaaro-Peled and colleagues.[30]

in a cell autonomous mechanism, but is also influenced by non-neuronal cells such as microglia and astrocytes.[10] In the cerebral cortex, dopaminergic projections from the midbrain region undergo alterations, accompanied by increases in dopamine levels until late adolescence.[11,12] Response to γ-aminobutyric acid (GABA)-ergic neurons also critically changes during adolescence.[13] An increase in myelination is prominent in late adolescence to young adulthood as well, which is associated with overall changes to molecular expression profiles.[14,15]

At the physiological level, the dynamics of neuronal activity changes during adolescence as cortical regions are formed into functional networks. There is also increased synchrony at multiple brain wave frequencies as well as changes in the balance between excitatory and inhibitory synapses (E/I balance).[16] Neuronal oscillations, particularly at gamma-band frequencies, may play an important role in cognitive and behavioral responses, such as perceptual grouping, attention-dependent stimulus selection, working memory, and consciousness.[17]

3. Critical periods

The classic concepts in neuropsychology that describe multiple developmental stages can be applied to the concepts of critical periods in neuroscience. The notion of the critical period originated from the observation by Wiesel and Hubel that monocular light deprivation during the neonatal stage resulted in blindness that could not be recovered by light exposure later in life, despite no prior intrinsic anatomical or biological abnormalities.[18] Recent studies in molecular neuroscience have indicated that there are indeed critical developmental windows governed by several concrete molecular factors: molecules associated with GABA neurotransmission and some immune-related molecules have been underscored.[19,20]

Experimental validation of critical periods has encouraged investigators to extend this approach to understand how stress during the critical period may even create vulnerability and resilience to psychopathology, and affect behaviors in later stages. Adolescents show an attenuated fear memory and extinction, suggesting that adolescence is indeed a sensitive period to stress that differs from other developmental and adult stages.[21] One study found that adolescents with anxiety disorders show a decreased responsiveness to cognitive behavioral therapy (CBT) compared to children and adults.[21] This susceptibility is associated with age-specific changes in neuroplasticity in the prefrontal cortex. Alterations to the neural regulation of fear and anxiety in adolescence, when paired with early life stress, can lead to a heightened "vulnerability to pathogenic experiences".[21] Yet, the unique molecular expression profiles and limited temporal window of adolescence allows clinicians to develop personalized treatment based on the patient's genetic profile and age.

As we described above, dopaminergic projections, particularly mesocortical projections, mature during adolescence. Disturbance of this maturation by adverse events during adolescence is experimentally proven to be causal for aberrant animal behavior, such as deficits in information processing, mood control, and psychostimulant hypersensitivity.[22] Investigators have elucidated that excess stress hormones, such as glucocorticoids, mediate this disturbance in adolescence.[22] By altering the timing of blockade against the activated glucocorticoid receptor signaling, we can determine how the critical period links hypothalamic-pituitary-adrenal (HPA) axis-associated dopaminergic disturbance and aberrant behavior in adulthood.[23] In addition, maturation of cortical myelination occurs in adolescence, and disturbances to this maturation process may

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