Neuroscience and Biobehavioral Reviews 70 (2016) 329–333

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Commentary on the special issue on the adolescent brain: Adolescence, trajectories, and the importance of prevention

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ARTICLE INFO

Article history:
Received 16 May 2016
Received in revised form 22 June 2016
Accepted 12 July 2016
Available online 14 July 2016

Keywords:
Adolescence
Adversity
Amygdala
Anxiety
Inflammation
Prefrontal cortex
Puberty
Salience
Stress

ABSTRACT

Adolescence as highlighted in this special issue is a period of tremendous growth, synaptic exuberance, and plasticity, but also a period for the emergence of mental illness and addiction. This commentary aims to stimulate research on prevention science to reduce the impact of early life events that often manifest during adolescence. By promoting a better understanding of what creates a normal and abnormal trajectory, the reviews by van Duijvenvoorde et al., Kilford et al., Lichenstein et al., and Tottenham and Galvan in this special issue comprehensively describe how the adolescent brain develops under typical conditions and how this process can go awry in humans. Preclinical reviews also within this issue describe how adolescents have prolonged extinction periods to maximize learning about their environment (Baker et al.), whereas Schulz and Sisk focus on the importance of puberty and how it interacts with stress (Romeo). Caballero and Tseng then set the stage of describing the neural circuitry that is often central to these changes and psychopathology. Factors that affect the mis-wiring of the brain for illness, including prenatal exposure to anti-mitotic agents (Gomes et al.) and early life stress and inflammation (Schwarz and Brenhouse), are included as examples of how exposure to early adversity manifests. These reviews are synthesized and show how information from the maturational stages that precede or occur during adolescence is likely to hold the key towards optimizing development to produce an adolescent and adult that is resilient and well adapted to their environment.

1. Introduction

Adolescence is an important transitional period of social development, risk-taking, and preparation for the independence of adulthood (reviewed by van Duijvenvoorde et al., 2016). Adolescence is also a period when mental illness and addiction appear (Paus et al., 2008; Kuhn, 2015). Often, these challenges emerge from a latent past of early traumatic events, drug exposure, or both (De Bellis, 2002; Andersen and Teicher, 2009). The reviews in this special issue comprehensively describe how the adolescent brain develops under typical conditions (Kilford et al., 2016; Caballero and Tseng, 2016), but also how early antecedent events may already have mis-wired the brain for illness long before it arrives at this stage. Factors that influence the trajectory of brain development are discussed in this issue, including stress (Romeo, 2016), sex hormones (Schulz and Sisk, 2016), and inflammation (Schwarz and Brenhouse, 2016). This commentary discusses the importance of understanding typical developmental processes to encourage research on prevention to reduce the impact of early life events on adolescence (Stanis and Andersen, 2014).

2. The shape of the trajectory matters

The process of maturation leading to adulthood requires that a number of processes, including cognitive, reward, social, and hormonal, come together at the right time. Events that occur during critical periods lay a foundation and later influences of the environment during a sensitive period shape the final trajectory. Derailing this process at either the critical or the sensitive period stage will have a significant impact to a yield a different trajectory of development (Paus et al., 2008; Andersen and Teicher, 2008). As a result, the emergence of depression, addiction, and other serious mental illnesses (e.g., schizophrenia and bipolar illness) often occurs during adolescence.

The interactions of many different factors culminate during the periadolescent period to shape the brain (Spear, 2000; Andersen, 2003). The timing of this peak in development depends on the measure (e.g., receptors, synapses, functional activity), the region of the brain, and the sex of the subject (reviewed by Brenhouse

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http://dx.doi.org/10.1016/j.neubiorev.2016.07.012
0149-7634/

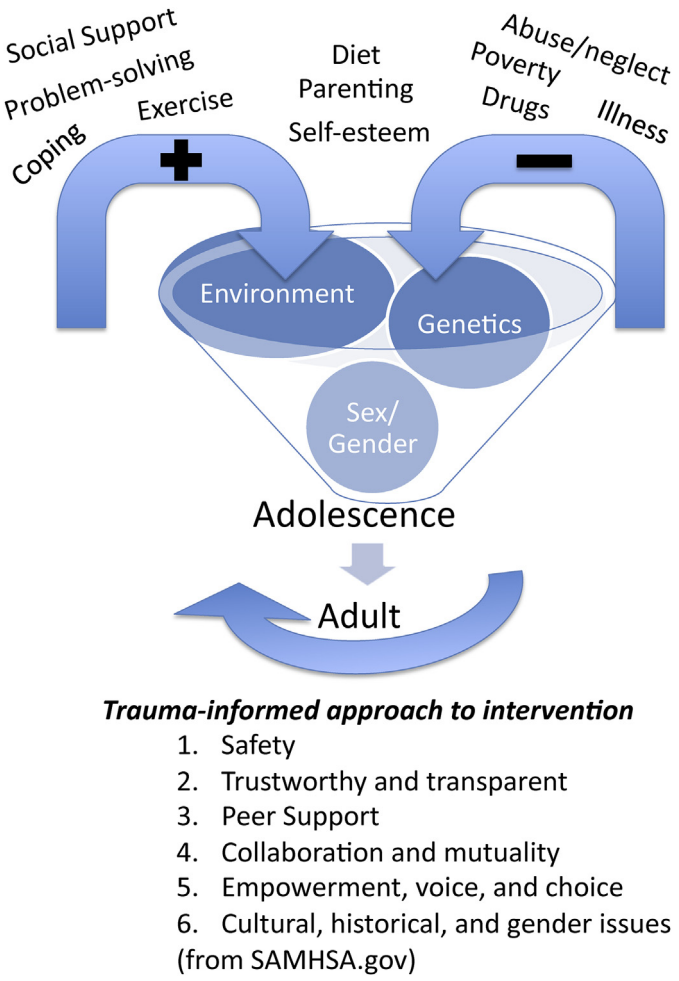

Fig. 1. Protective and risk factors interact with foundational developmental processes to produce an adolescent leading into an adult. Trauma-informed interventions may bridge the gap between negative and positive influences.

and Andersen, 2011a). Since its initial introduction in human post-mortem studies (Huttenlocher, 1979), the phenomenon of overproduction and later elimination is now a widely accepted process of brain development. However, less attention has been paid to the progressive increase in the underlying factors that support the transitions between prenatal life, childhood, and adolescence. By examining the trajectory of development, we know that some disorders can be characterized by differences in the rate to reach a final synaptic density. For example, the prefrontal cortex (PFC) shows delayed development (e.g., pruning) in attention deficit hyperactivity disorder relative to normal, age-matched controls (Shaw et al., 2007). Exposure to early adversity (poor parenting, neglect, abuse, poverty, drugs) also alters development, but in this case the trajectory reflects accelerated development (Andersen and Teicher, 2008) to serve an adaptive function to survive in a malevolent world (Teicher, 2002). Regardless of the impetus for the change (genetic, environmental, or their interaction; Fig. 1), clues lie within these altered trajectories that can inform improved outcomes of at-risk or affected teenagers.

3. Early developmental processes leading up to adolescence

The progressive rise of neural infrastructure (neurons, glia) shapes and guides development, "locks it in" during critical periods (Hensch, 2005), and provides a foundation for a lifetime (Gogolla et al., 2009). Critical periods occur in concert with active brain growth (requiring growth factors) where the balance between excitatory and inhibitory activity is important (Huang et al., 1999; Hanover et al., 1999). Most of what we know is based on the visual system (Webster et al., 2002; Lein et al., 2000) where critical periods are closed by excess glutamatergic activity or decreased GABA activity (Fagiolini and Hensch, 2000; Fagiolini et al., 2004). If a significant event occurs during this time – positive or negative – the individual will show a permanent predisposition towards a set of behaviors. Critical periods are also evident in other functions where the optimal period occurs prior to adolescence – before age 12 for more complex behaviors. Experts suggest that learning music (Trainor, 2005), a foreign language with the correct accent (Flege et al., 1995) or sports (Tonnessen et al., 2015) is optimal before this age. Anxiety, which has early seeded roots in early childhood (reviewed by Tottenham and Galvan, 2016), influences the development of depression. Factors that shape vulnerability to schizophrenia or addiction likely preceded their adolescent emergence by a more than a decade. Such factors include exposure to anti-mitotic agents prenatally (Gomes et al., 2016), stress (Romeo, 2016; Schwarz and Brenhouse, 2016; Tottenham and Galvan, 2016), inflammation, gonadal hormones (Romeo, 2016; Schulz and Sisk, 2016), which all contribute to mental illness and are discussed below and in this edition.

As critical periods are integral for the foundation of building a brain, sensitive periods occur when the brain is uniquely sensitive to environmental impacts. Such increased salience to environmental events is especially heightened during adolescence (Brenhouse et al., 2008; Sonntag et al., 2014; Lichenstein et al., 2016 [this edition]). Adolescents are more sensitive to peer relationships (Kilford et al., 2016 [this edition]), rewarding stimuli such as drugs of abuse and alcohol, seeking novelty in general, or sexual activity (Steinberg, 2008). Reduced levels of some of these behaviors may lead to a depressive phenotype, and too much of these behaviors can be lead to addiction, early pregnancy, or even premature death. An appropriate level of salience attributed to the environment will lead to independence, reproductive fitness, and other behaviors necessary for individuating during this stage (Spear, 2000; Steinberg, 2008; Luna et al., 2015). The anterior cingulate cortex and its inter-relationships with other brain regions play an important role in a number of these functions, and is described as the hub by Lichenstein et al. (2016). To demonstrate how salient memories are made during adolescence, think about what you remember from high school relative to childhood or later (more recent) stages in your life. Good or bad, high school was quite salient.

Mechanistically, we have determined that the over-expression of the D1 dopamine receptor in the prelimbic PFC projections plays a significant role in increased motivational salience during adolescence (Brenhouse et al., 2008). Briefly, animals with high-D1 expression had elevated novelty preferences, increased preferences for cocaine-, nicotine-, and alcohol-associated environments, increased self-administration of cocaine and the motivation to do so, and impulsivity (Sonntag et al., 2014). High-D1 receptors in the prelimbic PFC also increased sexual activity or lead to its reduction when D1 receptors were normalized (Freund et al., 2016). However, when D1 receptors were no longer elevated (and salience reduced), the animals demonstrated depressive behavior (Freund et al., 2016). These data show how motivational salience plays a vital role in heightening adolescent behaviors during this sensitive period.

Once an adolescent forms an association between the behavior and the environment/cue, a process that requires salience, the association is more difficult to change compared with other maturational stages. In this edition, Baker et al. (2016) reports on how extinction learning of fear-related stimuli is uniquely impaired during adolescence; prolonged extinction in adolescence relative to other stages is also observed to cocaine-associated environments