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

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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

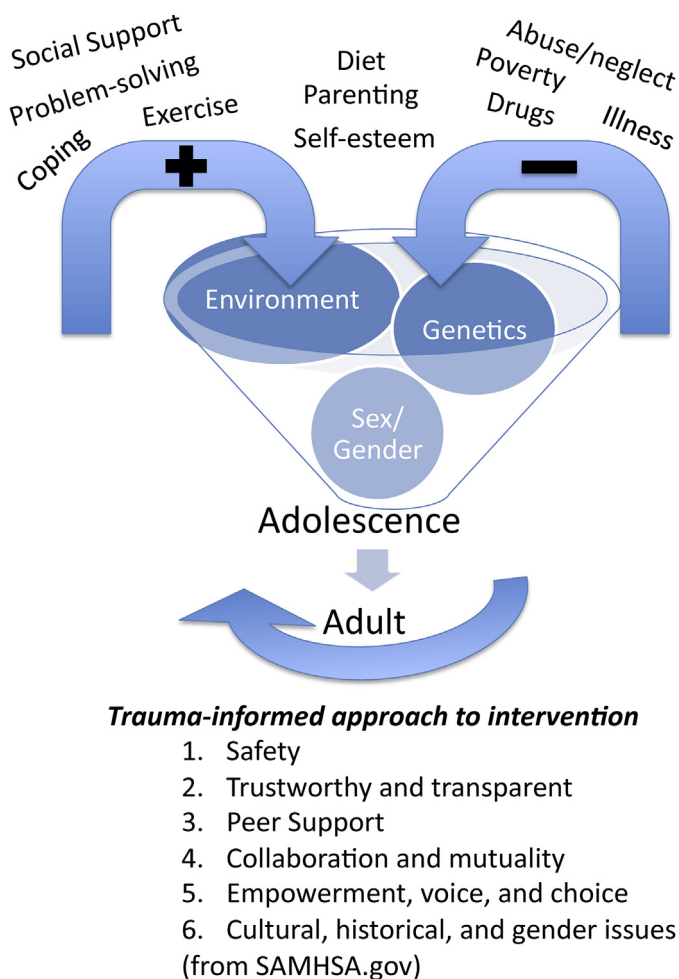*E-mail address:* sandersen@mclean.harvard.edu

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

(Brenhouse and Andersen, 2008), but see Li and Frantz (2009). This process is also related to motivational salience mediated by D1 receptors (Brenhouse et al., 2015). Taken together, these studies imply a period of enhanced learning about environmental factors that are made more salient during adolescence and are further accompanied by reduced extinction. As a result, associations that occur during adolescence or beforehand will become an important part of the individual's foundation for the rest of his/her life.

4. Sex differences and puberty onset

Schulz and Sisk (this edition, Schulz and Sisk, 2016) remind us that gonadal hormones strongly influence adolescent brain development. Dogma taught us that gonadal hormones influence the brain at two discrete time periods with two unique functions: perinatal hormones organize sex differences and pubertal hormones activate sex differences (Phoenix et al., 1959). However, the current thinking is that the inter-relationship of brain development and sex steroids is more continuous and represents a protracted sensitive period of development. From this perspective, paying attention to sex differences as they *continue* to emerge across childhood into adolescence is key for proper development. Puberty is a time of reproductive maturation (Schulz and Sisk, 2016), and mammals prepare by increasing risk-taking and social behaviors. The gonadal hormones play a role in shaping the adolescent brain. Imaging studies demonstrate sex differences in cortical gray matter (Giedd et al., 1997), and more detailed cell counts in the PFC of rats indicate estrogen increases neuronal loss during puberty that is prevented by ovariectomy (Juraska and Markham, 2004; Markham et al., 2007). Alterations in gonadal hormone expression leading up to adolescence as a result of early life stress (ELS; e.g., such as delayed puberty; Wilson et al., 2013) may have profound effects on brain structure. The review by Romeo (2016) discusses important sex differences to external stressors as a function of age and how they influence later adult function.

5. Early life stress and delayed clinical outcomes

Early life stress in the form of childhood abuse affects approximately one-third of the population, making it not only one of the most prevalent issues facing society, but also one of the most preventable. Four possible outcomes to ELS have been described: resilient, recovering, delayed, or chronically internalizing (e.g., anxiety or depression) or externalizing behaviors (e.g., impulsivity, aggression, self harm) (Bonanno and Mancini, 2008; D'Andrea et al., 2012). Together, these four potential outcomes imply different trajectories. The periadolescent period (11–12 years of age) is when abused and controls start to diverge in their developmental trajectories (Andersen and Teicher, 2008; Widom et al., 2007). A number of authors in this edition discuss how ELS produces altered trajectories that manifest during adolescence.

Studies on the effects of ELS on behavior and brain development suggest that a delay occurs in their manifestation, which is typically adolescence. For example, few depressive symptoms are observed in childhood following ELS, but are delayed an average of 9 years after the initiation of abuse (Widom et al., 2007; Teicher et al., 2009). The average of addiction, an externalizing disorder, can be as young as 12–13 years of age in children with low protective factors (including exposure to ELS and increases prevalence in nonvulnerable populations (Andersen and Teicher, 2009; Harrington et al., 2011)). A number of antecedent factors influence maldevelopment (Fig. 1) that lead up to an adolescent manifestation. Such a delay provides a window of opportunity for a targeted, preventative intervention for children exposed to ELS. However, we need more research on which factors can predict the trajectory of ELS.

Anxiety maybe one such factor to predict the internalizing disorder of depression. Approximately two-thirds of children with generalized anxiety disorder will develop depression in early adolescence (Beesdo et al., 2007). This same has been observed in victims of abuse (Andersen and Teicher, 2008).

Typical adolescents demonstrate progressively increasing social awareness that is observable in both behavior and with brain imaging studies (reviewed by Kilford et al., 2016 [this edition]). For example, typical adolescents demonstrate a hyper-responsivity to emotional faces (Monk et al., 2003; Killgore et al., 2001). Individuals with a history of ELS, however, show elevated amygdala activity to faces at <11 years old (Malter Cohen et al., 2013; Marusak et al., 2015), suggesting early maturation of this trajectory. Tottenham and Galvan (this edition; Tottenham and Galvan, 2016) comprehensively describe the inter-relationships between the amygdala and the prefrontal cortex in normal and abused subjects.

Altered trajectories have also been described in brain structure. Exposure to stress shows a loss in hippocampal volume that does not manifest until adolescence (De Bellis et al., 2001). With a more fine-tuned analysis of the timeline, synaptic density fails to peak at postnatal day 60 (P60) in a rat model of ELS (Andersen and Teicher, 2004). Changes in brain structure following ELS have been associated with different sensitive periods in the brain, where ages of active growth for a region are most vulnerable if the abuse occurs during that time (Andersen et al., 2008; Pechtel et al., 2014). Differences in myelination in general and more specifically, microglia (Schwarz and Brenhouse, 2016; Calcia et al., 2016), have also been described following ELS (Teicher et al., 2004). The relationship between altered myelination or functional connectivity are found in major depressive disorder or addiction; a meta-analysis of this inter-relationship is described in this edition by (Lichenstein et al., 2016).

6. Animal models and stress responsiveness

Preclinically, animal studies can model early adversity, including early shock treatments, maternal separation, and social isolation and defeat paradigms (reviewed by Andersen (2015)). Resultant behaviors following exposure to these paradigms are relevant to clinical findings described above (Andersen, 2015). For example, exposure to maternal separation increases depressive-like behaviors during adolescence that includes a reduction in synaptic density and myelin basic protein (Leussis and Andersen, 2008; Leussis et al., 2012). Animal modeling of a complex issue like child abuse in the human condition provides a simpler system to dissect out contributions of different systems that may contribute to psychopathology. The review by Romeo (this edition; Romeo (2016)) tells us that stress responses (measured by adrenocorticotropin hormone [ACTH] and corticosterone) in pre-pubertal rats (28 days of age) are protracted, but then becomes increasingly regulated by emerging adulthood (77 days of age). Here, the typical trajectory is one of increased stress regulation with maturation between peri-adolescence to adulthood. Sex differences also are important for stress effects. Females tend to show elevated stress responses following prior stress exposure and males show reduced stress responses, which are discussed in detail. Romeo reviews the stress responsiveness data from various animal models of stress exposure in this edition. These data highlight the importance of a derailed trajectory that can be used to guide an intervention by determining when regulatory processes diverge between conditions.

7. Sex differences in immune response to ELS

Immune responses are elevated in individuals with a history of ELS in humans (Carpenter et al., 2010) and animals (Brenhouse and Andersen, 2011b; Hennessy et al., 2015). The review provided by Schwarz and Brenhouse (2016) emphasizes how important sex differences can be for the expression of early life events. Adolescent activity in neuro-immune signaling pathways provides a novel mechanism possibly underlying sex differences associated with ELS. The majority of research focuses on the inflammatory markers of interleukin-6 (IL-6) and IL-1 beta, which are both increased following ELS exposure (Brenhouse and Andersen, 2011b). Following ELS, males express more interleukin-10 (IL-10) that protects against neuroinflammation than females (Schwarz and Brenhouse, 2016). Inflammatory responses have been associated with depression in adult human studies (Lindqvist et al., 2009) and these data suggest a potential protective factor against depression that is present in males. Here, we should not only focus on potential resilience factors, but utilize them strategically. By examining how such factors diverge across sex, sex differences can provide a novel perspective for prevention efforts. Preventative interventions are possible. For example, Wieck et al. (2013) have reported that central administration of IL-10 can prevent GABAergic losses that are found in animals exposed to ELS. Similar anti-inflammatory intervention studies where humans (Licinio and Wong, 1999) and animals (Brenhouse and Andersen, 2011; Hennessy et al., 2015) are treated with an anti-inflammatory have reduced depression or improved working memory.

8. Preventative interventions

As the study of adolescence moves forward, there needs to be a greater emphasis on prevention. Adolescence is the pinnacle of brain development and may be the last point for any permanent change before a sensitive period closes. For example, teens do not leave their house before the brain has reached such a peak, giving parents a last chance to provide both structure and guidance to their offspring. As information about typical and atypical behavior and brain development is presented in this edition, consider how knowing the number of well-validated, evidenced based factors that are used in prevention research can be applied to developing better interventions to prevent later dysfunction. The factors that improve interventions are: 1) age-related patterns of competence and disorder; 2) developmental-appropriate tasks; 3) multiple contexts to increase generalization; and 4) interactions among biological, psychological, and social factors. For example, cognitive behavior therapy is helpful for insight regarding trauma and how to move forward. These same skills can be taught to children and adolescents at any stage to improve everyday problem solving. The process of mentalising, perspective-taking, and social decision-making all use different parts of the brain that are increasing activated during adolescence (described by Kilford et al., 2016 [this edition]). Resultant endpoints include empathy, trust, perspective, reading social cues, and other social cognitive behaviors that lead to socially appropriate level of behavior. Trauma-informed therapies (Fig. 1) can bridge the divide between negative environmental factors that influence development and the positive ones that optimize it. Individuals with a history of ELS have difficulty in these domains and for good reason. The increasing social awareness (salience) that emerges during adolescence may be part of the trigger for the appearance of psychopathology during this period. However, such increased awareness may also be used therapeutically to alter brain connectivity by guided interventions. Exercise is another potential preventative intervention. Both animal and human studies show reduced rewarding effects of drugs and improved mood (Zlebnik et al., 2012; Norris et al., 1992; Nabkasorn et al., 2006) following exercise. Alternatively, reducing other risk factors, such as inflammation, can reduce the effects of ELS (Schwarz and Brenhouse, 2016; Brenhouse and Andersen, 2011b). Inflammation can be controlled by improved sleep, diet, exercise, or medication (Cotman and Berchtold, 2002; Kiecolt-Glaser et al., 2015; Schuch et al., 2016). The first two factors may also contribute to additional vulnerabilities of even typical adolescents.

9. Future considerations

If the goal of a researcher is to understand a phenomenon, and the goal of the clinician is to use any and all information to improve the well-being of their patient, then our fields need to move closer together to streamline this process. First, more cross talk is needed between these different groups to better understand the problem. Second, we need to find methodological points that facilitate cross talk among different species. Neuroimaging holds such promise for this goal, although task-based assessments in small mammals have not been achieved to the same level as humans. Saliva sampling represents another point for cross talk. Saliva sampling has been used at different ages (infants to the elderly) to measure cortisol/corticosterone or estrogen/testosterone have been assayed. Genetic and epigenetic measures are equally possible from saliva samples. Blood/plasma sampling represents another point of communication. Third, behavior provides another bridge and the Research Domain Criteria (RDocS) of the National Institute of Mental Health can guide cross talk. Brain/behavior changes that characterize adolescence are universal, and it is possible to alter the trajectory.

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