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Review

Puberty and adolescence as a time of vulnerability to stressors that alter neurobehavioral processes

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ABSTRACT

Puberty and adolescence are major life transitions during which an individual's physiology and behavior changes from that of a juvenile to that of an adult. Here we review studies documenting the effects of stressors during pubertal and adolescent development on the adult brain and behavior. The experience of complex or compound stressors during puberty/adolescence generally increases stress reactivity, increases anxiety and depression, and decreases cognitive performance in adulthood. These behavioral changes correlate with decreased hippocampal volumes and alterations in neural plasticity. Moreover, stressful experiences during puberty disrupt behavioral responses to gonadal hormones both in sexual performance and on cognition and emotionality. These behavioral changes correlate with altered estrogen receptor densities in some estrogen-concentrating brain areas, suggesting a remodeling of the brain's response to hormones. A hypothesis is presented that activation of the immune system results in chronic neuroinflammation that may mediate the alterations of hormone-modulated behaviors in adulthood.

1. Introduction

Puberty is a major life transition from that of a non-reproductive juvenile into a reproductively competent adult. Puberty and adolescence, the developmental period associated with puberty, are times of great physiological, psychosocial and cultural changes. As such, puberty and adolescence are also times of great developmental plasticity (Dahl and Gunnar, 2009; Patton and Viner, 2007). The neuroplasticity of puberty may also contribute to vulnerability for the development of mental diseases (Andersen, 2003). The National Comorbidity Survey Replication study, which assessed over 9000 people representative of the US population, indicate that affective disorders such as anxiety, bipolar disorder, and major depression emerge during adolescence, with the peak age of onset for these diseases of 14 years (Kessler et al., 2005; Paus et al., 2008). A major predictor of an individual's susceptibility to mental disease is his or her sex: women show higher rates of anxiety and depression, and men have higher rates of autism spectrum disorders, schizophrenia, and attention deficit hyperactivity disorder (Astbury, 2001; Eaton et al., 2012). However, the 2:1 female–male prevalence in depression and anxiety disorders emerges only after puberty (Angold and Costello, 2006). Moreover, the pubertal status (Tanner Stage III) predicts this sex difference better than age alone (Hayward and Sanborn, 2002; Patton et al., 1996), suggesting that ovarian hormones, particularly in puberty/adolescence, play a role in the etiology of affective disorders.

Recently, studies have demonstrated that peri-pubertal or adolescent exposure to stressful life experiences contributes greatly to an individual's vulnerability to mental disease (Ge et al., 2001; Grant et al., 2003, 2004; Silverman et al., 1996; Turner and Lloyd, 2004). Yet little is known about how stress could disrupt normal neural development during the pubertal or adolescent period to produce a brain that is particularly vulnerable to mental diseases. Therefore, it is important to understand the neural mechanisms by which a pubertal stressor may produce a brain that is susceptible to specific mental diseases. Using animal models, we are beginning to learn the unique ways in which a pubertal organism responds to a stressor, and how the experience of stressors during pubertal development alters adult physiology and behavior.

The focus of this review is to present results of recent studies that demonstrate (i) that stressors experienced in puberty alter steroid hormone-influenced behaviors in adulthood and (ii) that these behavioral changes may be mediated through alterations in the ongoing processes of brain development. First, we provide a short background on some of the major developmental processes that occur during puberty and adolescence. Next, we discuss the ability of stressors during pubertal development to alter the display of sexual behaviors, anxiety- and depression-like behaviors, and learning, memory and cognitive behaviors, giving special

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attention to the possible neural correlates and mechanisms of these behavioral responses. Finally, we postulate a novel mechanism by which stressors may act to achieve enduring effects in the adult brain and behavior.

2. Puberty and adolescence

2.1. Definitions of puberty and adolescence

Puberty and adolescence are commonly conflated; however, in order to understand the ways that puberty and adolescence can influence the brain's response to hormones, it is critical to disambiguate and use precise definitions of both puberty and adolescence, as they are distinct processes. Puberty refers to the developmental transition from a non-reproductive state into a reproductive state, culminating in reproductive competence (Sisk and Foster, 2004; Waylen and Wolke, 2004). Even though it is sometimes referred to as a singular event, puberty is a prolonged, developmental process. The term is not only used to indicate the attainment of reproductive competence, but also it is used to describe the reproductive changes culminating in reproductive competence. Throughout this review, we will refer to the changes that occur in reproductive status as pubertal developments and the time during which these pubertal developments occur as the pubertal period. In contrast, adolescence refers to the social and cognitive maturation associated with and resulting from the hormonal changes of puberty (Sisk and Foster, 2004). While the biological hallmarks of pubertal development have been extensively categorized as the Tanner Stages, the biological hallmarks of adolescence are more nebulous and include the neuroplasticity and development of the cortical and limbic areas of the brain.

Pubertal development in humans comprises several physiological and physical changes (Fig. 1), including the development of secondary sexual characteristics (e.g., breast budding in girls and testicular enlargement in boys and the growth of pubic hair) and culminating in the onset of reproductive competence (e.g., menarche and ovulatory menstrual cycles in girls and semenarche and spermarche in boys) (Marshall and Tanner, 1969, 1970; Tanner, 1962). The pubertal processes are dependent on the presence of estrogens and progestins in girls and androgens in boys (Tanner, 1962). Typically girls begin pubertal development around ages 10–11 and have completed the process by ages 15–16 (Marshall and Tanner, 1969; Tanner, 1962), whereas boys begin puberty slightly later at ages 11–12 and have completed it by 16–17 (Marshall and Tanner, 1969; Tanner, 1962).

In female rodents, the first stage of pubertal development is typically the first external sign of ovarian activity (i.e., vaginal opening), and puberty is considered complete with the onset of the first reproductive (i.e., estrous) cycle. Although variable and dependent on housing conditions (e.g., Vandenbergh, 1967, 1969), the day of vaginal opening is approximately postnatal day 35 (P35) in rats (Ojeda and Urbanski, 1994; Ojeda et al., 1976) and P25 in C57Bl/6 mice and P30 in CD1 mice housed in single

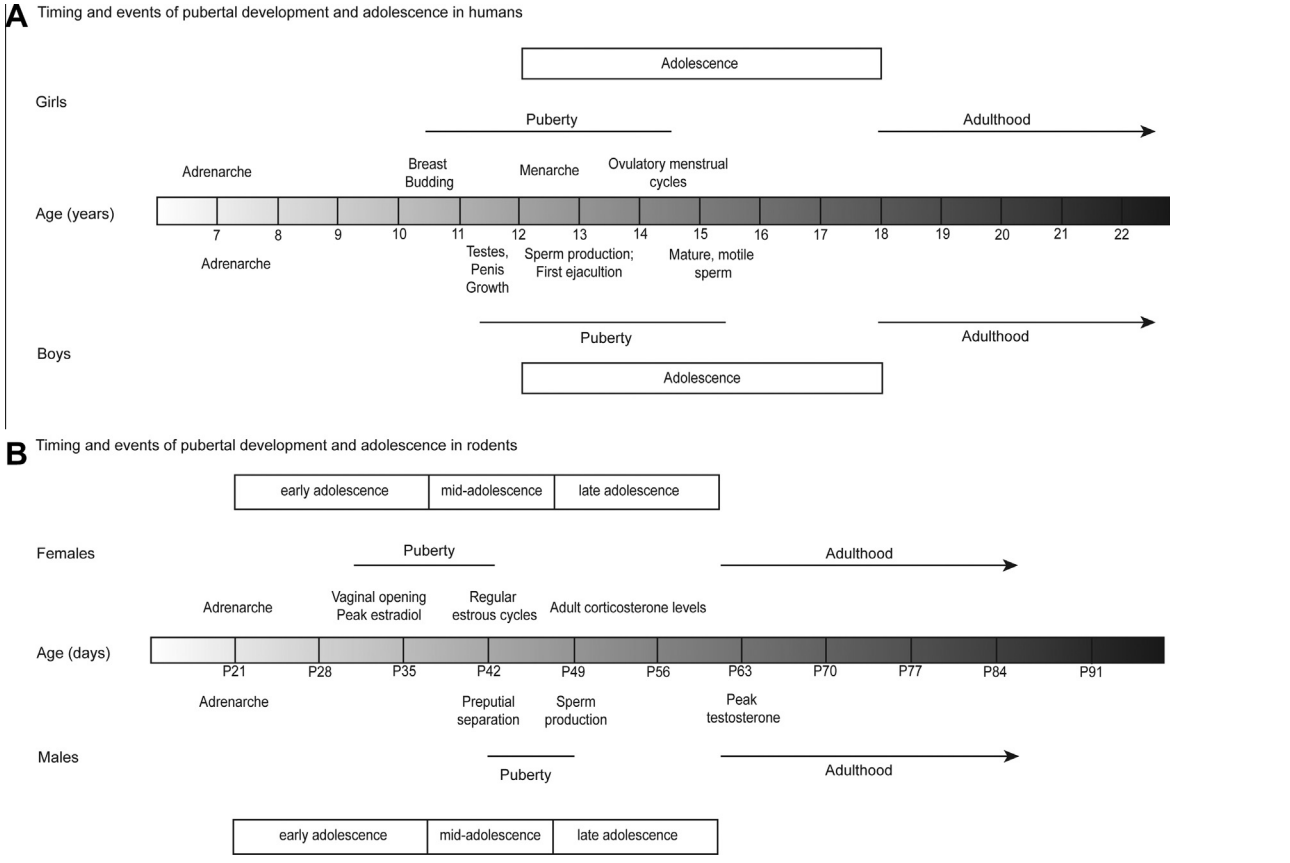

Fig. 1. A generalization of the approximate timing and events of pubertal development and adolescence in (A) humans and (B) rats. (A) The average ages of the pubertal developments for girls (top) and boys (bottom) (Marshall and Tanner, 1969, 1970; Sizonenko, 1989; Tanner, 1962) and for (B) females (top) and males (bottom) (Korenbrot et al., 1977; Lohmiller and Sonya, 2006; Ojeda and Urbanski, 1994; Ojeda et al., 1976; Parker and Mahesh, 1976; Vandenbergh, 1967, 1969). Puberty onset is defined by the appearance of the secondary sex characteristics, and the offset is defined by the emergence of reproductive competence as indicated by ovulatory menstrual cycles and mature, motile sperm. In humans, the ages ranging from 12 to 18 are commonly used as the age range of adolescence (Spear, 2000); whereas, in rats adolescence is conceptualized by early, mid, and late adolescent periods (Tirelli et al., 2003). It should be noted that the times indicated for particular stages are quite variable, and can be influenced by nutrition and environmental conditions.