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A systematic review of adrenarche as a sensitive period in neurobiological development and mental health

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ABSTRACT

Substantial hormonal and neurobiological changes occur during puberty, and are widely argued to render this period of life a sensitive period in terms of risk for mental health problems. However, there is a paucity of research focusing on adrenarche, the earlier phase of pubertal development. Furthermore, there is a limited understanding of the association between adrenarche and neural development during this phase of life. We systematically reviewed research examining human adrenarcheal development as operationalized by hormonal levels of DHEA and DHEA-S, in relation to indices of mental health (Systematic Review 1). We then reviewed the limited amount of literature that has examined the association between adrenarcheal development and brain structure or function (Systematic Review 2). In general, studies showed that earlier timing of adrenarche was associated with greater mental health symptoms, and there is emerging support that brain development plays a role in this relationship. However, several methodological inconsistencies were noted. We propose that future research in this area test a theoretical model of adrenarche as a sensitive period of neurobiological development, whereby timing of exposure to hormones interacts with brain development, biological sex, and psychosocial stress to influence environmental sensitivity and risk for mental health problems through adolescence.

Contents

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1. Introduction

Substantial changes occur during puberty, including social and physical development, increases in hormones and hormonal reactivity, and related neurobiological development. These changes are widely argued to render this period of life a sensitive period in terms of risk for mental health problems (Ladouceur et al., 2012; Paus et al., 2008). However, there are two separate phases in pubertal development: *adrenarche*, which is triggered by the maturation of the zona reticularis of the adrenal gland, and *gonadarche*, associated with the maturation of the hypothalamic-pituitary-gonadal axis. A link between puberty and mental health has been mainly demonstrated with respect to the second phase of pubertal development, gonadarche, which begins with the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus at approximately 10–11 years of age, and triggers a rise in testosterone and estradiol, the maturation of primary and secondary sexual characteristics, and menarche in girls (Dorn, 2006). Individual differences in puberty can be measured in three ways. First, pubertal status, the developmental stage at which an individual is at a given point of time, can be measured by physical characteristics such as Tanner stage. Tanner stage can be assessed via self-report, parent-report, or a physical examination by a physician. Second, pubertal timing, which is pubertal status relative to same-age and −sex peers, can be measured by comparing stage/status via physical characteristics to peers, or by comparing levels of pubertal hormones to peers. Third, pubertal tempo, which is how quickly an individual passes through pubertal stages, can be measured over time (i.e., longitudinally) to examine the rate of maturation via physical characteristics or levels of hormones. We note that there is a paucity of studies that examine pubertal tempo in relation to mental health. Pubertal stage (gonadarche), on the other hand, has shown to be associated with mental health (Angold et al., 1998; Oldehinkel et al., 2011), and, in particular, it is pubertal *timing* that appears to be especially salient in predicting the onset of mental health problems (e.g., Angold and Costello, 2006; Kaltiala-Heino et al., 2003b; Mendle et al., 2010), and may be associated with different symptoms compared to pubertal stage alone (Oldehinkel et al., 2011). Early timing of gonadarche has been associated with depression (Copeland et al., 2010; Graber et al., 2004), anxiety (Hayward et al., 1992; Patton et al., 1996; Zehr et al., 2007), and eating (Zehr et al., 2007) and behavioral disorders (Copeland et al., 2010; Lynne et al., 2007; Stattin and Magnusson, 1990), especially for girls (Ge et al., 2001b), while the evidence for boys is more mixed (Ge et al., 2001a; Graber et al., 1997; Kaltiala-Heino et al., 2003a).

1.1. Adrenarche in human development

Considerably less work has focused on how adrenarche, the earlier phase of pubertal development associated with a dramatic increase in the level of androgens secreted by the adrenal cortex, affects psychological and neural functioning. This is surprising given that 1) early timing of adrenarche is a known risk factor for poor physical health later in life (Ibáñez et al., 2006), and 2) adrenarche does not occur in species other than human beings and some higher primates (Conley et al., 2012), and therefore may have specific evolutionary significance that might be associated with patterns of neural development particular to these species. Adrenarche typically begins around five to seven years of age when levels of the androgens dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), secreted from the adrenal glands, begin to increase, before the hypothalamic-pituitary-gonadal axis is reactivated (Parker et al., 1978; Rainey et al., 2002; Remer et al., 2005). DHEA is converted to DHEA-S through a sulfation process and is also more stable as DHEA-S (Maninger et al., 2009). Adrenarche and gonadarche are separate periods that are activated and controlled by independent mechanisms (Counts et al., 1987). Importantly, the external physical changes associated with adrenarche (increased skin oil production, body odor, and skeletal maturation; Dorn and Chrousos, 1997) may not be obvious until well after the initial rise in adrenarcheal hormones has begun (Wan, 2012) and as of yet there are no references values for DHEA/DHEA-S that match the physical manifestations of adrenarche (Uçar, 2015). This means that measurement of these hormones as objective indications of this phase is vital for research examining adrenarche.

1.2. Possible links between adrenarcheal and brain development

Moreover, there is limited understanding of the association between adrenarche and neural development during this phase of life. However, it has been proposed that adrenarche serves an evolutionary purpose for humans to extend brain development and promote synaptogenesis for social learning that is necessary starting from this age (Campbell, 2006). Indeed, there is evidence suggesting that adrenarcheal hormones may be key factors in brain development during the transition from childhood to early adulthood. For example, animal research has demonstrated that DHEA and DHEA-S have pleiotropic roles in the brain including stimulating neurite growth and neurogenesis, modifying neural activity via direct and indirect effects (via conversion to testosterone, di-hydrotestosterone and estrogen) on pre- and post-synaptic receptor and binding sites, and neuroprotective effects (via anti-glucocorticoid, anti-oxidant and inhibition of apoptosis; Maninger et al., 2009). Rodent work has demonstrated that DHEA administration decreases cognitive impairments and putatively depressive behaviors by enhancing neurogenesis in the hippocampus (Moriguchi et al., 2013, 2011). In adults, administration of DHEA appears to reduce activity in the amygdala and hippocampus, enhance connectivity between the amygdala and hippocampus, and enhance activity in the rostral anterior cingulate cortex (rACC) during emotional processing and regulation (Sripada et al., 2013).

Furthermore, the timing of adrenarcheal hormones may follow patterns in brain development, suggesting that these hormones may have organizational and activation roles in the brain, although more research is needed. For example, DHEA-S levels are high at birth, decrease rapidly after birth, begin to increase again at the beginning of adrenarche around five to six years of age, and peak in the mid-20s (Rainey et al., 2002; Sulcová et al., 1997) – although it should be noted that other research has shown that DHEA begins to increase closer to seven years of age (Remer et al., 2005), or later depending on sex (Sulcová et al., 1997). Timing of adrenarche is variable, and in particular, consensus regarding def-