



Brain structural connectivity during adrenarche: Associations between hormone levels and white matter microstructure



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ABSTRACT

Levels of the adrenal hormones dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and testosterone, have all been linked to behavior and mental health during adrenarche, and preclinical studies suggest that these hormones influence brain development. However, little is known about how variation in these hormones is associated with white matter structure during this period of life. The current study aimed to examine associations between DHEA, DHEAS, and testosterone, and white matter microstructure during adrenarche. To avoid the confounding effect of age on hormone levels, we tested these associations in 87 children within a narrow age range (mean age 9.56 years, SD = 0.34) but varying in hormone levels. All children provided saliva samples directly after waking and completed a diffusion-weighted MRI scan. Higher levels of DHEA were associated with higher mean diffusivity (MD) in a widespread cluster of white matter tracts, which was partially explained by higher radial diffusivity (RD) and partially by higher axial diffusivity (AD). In addition, there was an interaction between DHEA and testosterone, with higher levels of testosterone being associated with higher fractional anisotropy (FA) and lower MD and RD when DHEA levels were relatively high, but with lower FA and higher MD and RD when DHEA levels were low. These findings suggest that relatively early exposure to DHEA, as well as an imbalance between the adrenal hormones, may be associated with alterations in white matter microstructure. These findings highlight the potential relevance of adrenarcheal hormones for structural brain development.

1. Introduction

Puberty is a crucial developmental phase marking the transition between childhood and adolescence. While there is much literature emphasizing the importance of pubertal processes for brain development (Goddings et al., 2014; Herting et al., 2017, 2012; Peper et al., 2011), these studies have focused on gonadarche and relatively little attention has been paid to the earliest phase of puberty: adrenarche. This is despite evidence that hormonal changes associated with adrenarche are important for behavior and mental health (Byrne et al.,

2017). Adrenarche starts at around 7–8 years of age and is initiated by the activation of the hypothalamo–pituitary–adrenal (HPA) axis that leads to marked increases of circulating androgens including dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), and testosterone (Styne and Grumbach, 2011). Testosterone, while commonly considered gonadal, is also metabolized in the adrenal zona reticularis and peripheral tissue after the conversion of DHEA to androstenedione, and thus levels rise with the onset of adrenarche (Rege and Rainey, 2012).

Much of what we know about the effects of adrenarcheal hormones

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on the brain comes from animal research. This work suggests that testosterone, DHEA and DHEAS have positive effects on neuronal growth and survival, and axon growth (Fargo et al., 2008; Maninger et al., 2009) and can have a long lasting impact on brain organization (Schulz et al., 2009). In particular, DHEA has been found to stimulate axon growth during fetal development, whereas DHEAS has been linked to growth and branching of dendrites (Compagnone and Mellon, 2000, 1998). However, we do not know how these findings translate to humans, and if they occur during the adrenarcheal period, since this developmental phase is thought to be unique to humans and great apes (Campbell, 2011a).

There is speculation that in humans the parallel timing of increased DHEA production and cortical thinning, both starting during late childhood, may indicate that DHEA influences brain maturation (Campbell, 2011b). A number of studies have now demonstrated links between both DHEA and testosterone, and gray and white matter structure in adolescents (i.e., during and beyond gonadarche). For example, in adolescents aged 10–16, Herting et al. (2015, 2012) found associations between increased testosterone and changes in caudate and amygdala volumes, decreases in frontal surface area in boys, and increases in frontal surface area in girls. Menzies et al. (2015) found an inverse association between testosterone and mean diffusivity in white matter across a number of tracts in adolescents aged 12–17.

Researchers have only recently started to elucidate how adrenarcheal hormones relate to brain structure during adrenarche (i.e., during mid-late childhood). Nguyen et al. (2013), in the only study of gray matter structure during adrenarche (to our knowledge), reported positive correlations between DHEA and cortical thickness in parts of the left frontal, right temporal and right parietal cortices in 4- to 13-year-olds. Only one study has examined DHEA levels during adrenarche in relation to white matter, utilizing the same cohort of children as in the current paper. This study found a negative correlation between DHEA and white matter volume in the anterior corona radiata (Klauser et al., 2015), the opposite association to what might have been predicted from animal research. To our knowledge, no studies have been conducted to investigate the association between adrenarcheal hormones and white matter *microstructure* during adrenarche.

Further, previous work has shown that interactions between hormones may also be important in predicting brain structure. While the adrenarcheal hormones tend to covary positively during adrenarche (Matchock et al., 2007), Nguyen et al. (2013) showed that the interaction between DHEA and testosterone was associated with cortical thickness in children such that a relative imbalance in the hormone levels was associated with reduced cortical thickness in the cingulate cortex and the occipital pole. However, it has not yet been examined how these hormones might interact to influence brain white matter structure during adrenarche.

What is now needed is an investigation of the role of multiple adrenarcheal hormones on white matter *microstructure* during *adrenarche*. Measures of microstructure offer far more nuanced information about the organization of white matter tracts, as opposed to simple volumetric measures. In the current study, we examined associations between DHEA, DHEAS and testosterone, and white matter microstructure in a community sample of children selected to vary widely in levels of these hormones. Given our previous work, we hypothesized that higher levels of these hormones would be associated with alterations in white matter microstructure that potentially indicate reduced white matter integrity. In addition, in order to help clarify the role of DHEA in white matter development, and based on the work of Nguyen et al. (2013), we investigated whether DHEA would interact with testosterone in its relation to white matter microstructure. Finally, although levels of the three hormones tend to be similar for boys and girls during adrenarche (Matchock et al., 2007), we explored the possible moderating role of sex.

2. Methods

2.1. Participants

Full details of the recruitment strategy and data acquisition can be found in the Imaging Brain Development in the Childhood to Adolescence Transition Study (iCATS) protocol (Simmons et al., 2014). Briefly, participants were invited to participate in iCATS if they were in the lowest or highest tertile of both DHEA and testosterone levels as measured in a larger parent project (Mundy et al., 2013). This served to maximize variance in hormone levels in the sample. Hormone levels at participation in iCATS correlated significantly with levels at recruitment (DHEA: $r = 0.70$, DHEAS: $r = 0.65$, testosterone: $r = 0.43$, all $p < 0.001$). Continuous measures of the hormones were used here instead of the tertile groups to get a more refined picture of the association of each of the hormones with white matter. Children were excluded from the study if they had a history of developmental or intellectual disorder as reported by parents/guardians, from the MRI scan if they had claustrophobia or non-removable ferrous metals in their body, and from analyses in the case of amphetamine based medication use at the time of hormone collection since this has been associated with alterations in brain structure (de Luis-García et al., 2015). The absence of an intellectual disability ($IQ < 70$) was further confirmed by an IQ estimate based on the two-subscale version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Parents/guardians also reported on medical conditions, and none of the participants had been diagnosed with premature adrenarche or gonadarche. Written consent was obtained from the parent/guardian and verbal consent from the child. Ethics approval was granted by the Royal Children's Hospital Human Research Ethics Committee (#32171), and ratified by the University of Melbourne Human Research Ethics Office (#1238745).

A total of 388 children who met inclusion criteria for the study were selected, and 128 of these agreed to participate in iCATS at the first assessment wave. Out of this group, 91 participants completed a Diffusion Weighted Imaging (DWI) scan and saliva collections. The main reason for non-completion was the parent or child being uncomfortable with MRI scanning ($n = 28$). One participant was removed due to movement artifacts and another participant due to late collection of the saliva (> 30 min after waking). In addition, two participants with extreme outlying values on the hormone levels were excluded (both were > 3 SD above the mean for DHEA). This resulted in a final sample of 87 participants (40 boys, 47 girls) with a mean age of 9.56 years ($SD = 0.34$, range 8.84–10.32 years).

2.2. Saliva collection and processing

Saliva samples were collected at waking on the day prior to, and on the day of scanning. Children collected 2.5 ml of saliva into a test tube via passive drooling and they recorded the time it took them to collect the saliva using a stopwatch. Samples were initially frozen at -30 °C, and prior to analysis, defrosted and centrifuged, with the supernatant assayed for levels of DHEA, DHEAS and testosterone using Salimetrics ELISA kits. For levels below the detection limit of kits (5.4% of the data; sensitivity = 5 pg/ml for DHEA, 43 pg/ml for DHEAS, 1 pg/ml for testosterone), the midpoint of the undetectable range was imputed. On average, samples were assayed within 7.72 weeks of collection. The inter-assay coefficients of variation (CV) were 5.45%, 7.53%, and 13.54% respectively and intra-assay CV 8.56%, 9.38% and 7.32% respectively. For more details on collection and processing of the saliva, see Simmons et al. (2014). An average measure from the two days was used for analyses (levels from the two samples correlated significantly: DHEA $r = 0.85$, DHEAS: $r = 0.87$, testosterone: $r = 0.65$, all $p < 0.001$).

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