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# Reduced frontal white matter volume in children with early onset of adrenarche

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**Summary** While there is growing evidence that puberty affects brain development, very little is known about the structural brain changes associated with dehydroepiandrosterone (DHEA), an adrenal hormone that exhibits dramatic increases during adrenarche, the earliest phase of puberty. Moreover, no research has investigated whether relatively early exposure to DHEA (i.e., early adrenarche) during this period is associated with differences in brain structure. We ran a whole-brain voxel-based morphometry analysis on T1-weighted magnetic resonance imaging brain scans to compare gray (GMV) and white matter volumes (WMV) between children experiencing relatively early ($n = 41$) vs. relatively late ($n = 44$) adrenarche. We also investigated the correlations between GMV or WMV and DHEA levels, and finally, tested for sex differences in group and correlation analyses. We observed reduced frontal WMV in a cluster located on the left corona radiata in children experiencing earlier adrenarche. In addition, WMV in this area was negatively correlated with DHEA levels. We did not observe any effect of gender in both the group and the correlation analyses. Early onset of adrenarche (as defined by relatively early exposure to DHEA) may be associated with differences in the development of frontal white matter tracts.


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## 1. Introduction

The onset of adolescence is biologically defined by puberty, a process that can in humans and some closely related higher primates be divided into early and late phases: adrenarche and gonadarche, respectively. Adrenarche is initiated by the activation of the hypothalamo—pituitary—adrenal (HPA) axis that eventually leads to marked increases of circulating androgens including dehydroepiandrosterone (DHEA) and its sulphated ester, dehydroepiandrosterone sulfate (DHEAS). Gonadarche refers to the maturation of the hypothalamo—pituitary—gonadal (HPG) axis that stimulates the production of sex hormones from the testes or ovaries.

Studies describing trajectories of brain development during puberty have shown that overall and regional gray matter volumes either decrease, or show an inverted-U shaped trajectory across childhood and adolescence (Shaw et al., 2008). Gray matter loss in fronto-temporal regions seems to approximate the whole brain pattern while in more caudal brain regions, a slight decline in gray matter appears to start from approximately age 5 (Aubert-Broche et al., 2013). In contrast, regional white matter development appears to be quite homogeneous, and all brain regions show a trajectory that is very similar to the overall white matter developmental pattern, that is, linear increases across childhood and adolescence (Mills and Tamnes, 2014).

While the vast majority of studies describing brain development during childhood and adolescence have described development as function of age (Giedd et al., 1999; Shaw et al., 2008; Aubert-Broche et al., 2013) recent research has also documented brain development in relation to pubertal stage, regarding gonadotropin levels (Peper et al., 2008) or sex steroids levels (Peper et al., 2009a). In addition to their independent effect on brain development, age and pubertal stage have also been shown to have interactive effects on the growth of subcortical structures (Goddings et al., 2014), suggesting the importance of considering pubertal timing (i.e., pubertal stage relative to age) for studying neurodevelopmental trajectories.

Differences observed in the developmental trajectories of gray and white matter between males and females (Lenroot et al., 2007; Perrin et al., 2008) could be related to earlier pubertal timing in girls relative to boys, although this sexual dimorphism is also certainly driven by differences in gonadal hormones (Neufang et al., 2009) and receptors expression (Perrin et al., 2008).

Among peers of the same sex, relatively early timing of puberty has been associated with increased risk for psychopathology in both males and females (Graber et al., 2004; Mendle et al., 2010). For example, in the context of depression, larger pituitary volumes were found to mediate the relationship between early timing of puberty and increased depressive symptoms in youths (Whittle et al., 2012). Nevertheless, only a few MRI studies have investigated associations between pubertal timing and brain development and most have focused on the later gonadarche period, when physical signs of puberty are easier to identify (Peper et al., 2009b).

Although the biological effect of adrenarchal hormones, such as DHEA, on brain development are still unclear, studies in rodents have reported that they can facilitate functional (Chen et al., 2006) and structural (MacLusky et al., 2004) synaptic plasticity mechanisms, as well as neurogenesis (Moriguchi et al., 2013) in the hippocampus. In humans, the parallel timing of increased DHEA production and extended cortical thinning, both starting during late childhood, raises the possibility that DHEA may be involved in synaptic pruning and more generally in brain maturation mechanisms that occur during pubertal development (Campbell, 2011). This is also consistent with a recent structural MRI study showing that cortical thickness was positively associated with salivary DHEA levels in several areas located in the prefrontal cortex, the parieto-temporal junction and the medial part of the temporal lobe, in prepubertal children aged from 4 to 13 (Nguyen et al., 2013).

There is no similar demonstration of a direct relationship between DHEA levels and white matter changes, although a recent longitudinal study has reported both an expansion, and optimization of white matter tracts from 9 to 12 years old, a time where adrenarchal processes are underway (Brouwer et al., 2012).

Taken together, there is some evidence from in vitro studies in animals that adrenarchal hormones could stimulate brain development by facilitating neuroplasticity mechanisms, but there is a lack of research in humans that has used appropriate methodology to assess the relation between adrenarchal timing (i.e., relative exposure to DHEA) and cerebral gray and white matter development.

We ran a whole-brain voxel-based morphometry (VBM) analysis on cerebral gray and white matter to assess the association between adrenarchal timing and brain structure in a sample of 9-year old children. Adrenarchal timing was assessed in two ways; first by early and late groups defined by relative DHEA levels at the time of recruitment, and second by DHEA measurements collected concurrent with an MRI brain scan approximately 6 months later. We hypothesized that the group with higher DHEA levels (i.e., early) would display regional differences in gray (GMV) and white matter volumes (WMV), with the early group showing relatively advanced maturation of local brain regions. In the context of the seminal work by Nguyen and colleagues that reported positive association between DHEA and cortical thickness in several brain regions, we expected that the group with higher DHEA levels (i.e., early) would display increased GMV in prefrontal, parietal and medio-temporal brain regions. Regarding white matter, we predicted that the high DHEA group would show increased WMV, given previous reports of continued white matter growth across childhood and adolescence (Lenroot et al., 2007; Aubert-Broche et al., 2013). We also anticipated positive correlations between DHEA levels and regional volumes in the same areas showing group-differences. We finally hypothesized that both group difference and correlation analyses would show a high degree of sexual dimorphism.

## 2. Materials and methods

Ethical approval was granted by the Royal Children's Hospital Human Research Ethics Committee (32171) and ratified by the University of Melbourne Human Research Office (1238745).