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Dehydroepiandrosterone impacts working memory by shaping cortico-hippocampal structural covariance during development

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ABSTRACT

Existing studies suggest that dehydroepiandrosterone (DHEA) may be important for human brain development and cognition. For example, molecular studies have hinted at the critical role of DHEA in enhancing brain plasticity. Studies of human brain development also support the notion that DHEA is involved in preserving cortical plasticity. Further, some, though not all, studies show that DHEA administration may lead to improvements in working memory in adults. Yet these findings remain limited by an incomplete understanding of the specific neuroanatomical mechanisms through which DHEA may impact the CNS during development. Here we examined associations between DHEA, cortico-hippocampal structural covariance, and working memory (216 participants [female = 123], age range 6–22 years old, mean age: 13.6 +/− 3.6 years, each followed for a maximum of 3 visits over the course of 4 years). In addition to administering performance-based, spatial working memory tests to these children, we also collected ecological, parent ratings of working memory in everyday situations. We found that increasingly higher DHEA levels were associated with a shift toward positive insular-hippocampal and occipito-hippocampal structural covariance. In turn, DHEA-related insular-hippocampal covariance was associated with lower spatial working memory but higher overall working memory as measured by the ecological parent ratings. Taken together with previous research, these results support the hypothesis that DHEA may optimize cortical functions related to general attentional and working memory processes, but impair the development of bottom-up, hippocampal-to-cortical connections, resulting in impaired encoding of spatial cues.

1. Introduction

Dehydroepiandrosterone (DHEA) rises steeply in children at the intersection of a critical cognitive developmental period, middle childhood (i.e. 6–8 years of age) and an important endocrine event, adrenarche (Campbell, 2011; Remer et al., 2005). This hormone remains at high levels throughout adolescence and young adulthood, only starting to decrease past the third decade of life (Adams, 1985). All this points toward a critical role for DHEA in both physical maturation and neurodevelopment throughout middle childhood and adolescence

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(Campbell, 2011). In fact, only humans, the great apes and certain types of Old World monkeys exhibit adrenarche, a key developmental event leading to increased production of DHEA (Remer et al., 2005), further bolstering the evolutionary importance of this hormone in primate-specific development. Recent genetic evidence confirms this hypothesis by demonstrating that DHEA affects gene expression relevant to energy allocation and homeostasis, alertness, and cell survival in the central nervous system (CNS) (Mo et al., 2009).

Existing studies of human brain development support the notion that DHEA may be involved in preserving cortical plasticity in brain networks involved in cognitive control, such as the left dorsolateral prefrontal cortex, right temporoparietal junction, right premotor and right entorhinal cortex, particularly in children age 4–13 years old (Nguyen et al., 2013b). Reports of DHEA administration in adults also outline beneficial effects on cognition overall, with a certain specificity for working memory and attention (Alhaj et al., 2006; Davis et al., 2008; de Menezes et al., 2016; do Vale et al., 2014). Recent findings from our group support some of these 'pro-cognition' effects of DHEA by showing that DHEA ameliorates visual attention processes by shaping amygdala-dependent cortical plasticity from childhood to young adulthood (Nguyen et al., 2016). More specifically, DHEA was found to be associated with structural covariance between the amygdala and the anterior cingulate, somatosensory and primary visual cortex (Nguyen et al., 2016). In turn, this DHEA-related structural covariance was related to improved performance on tests of visual awareness, visuo-motor dexterity and general level of attention (Nguyen et al., 2016). Still, not all studies are consistent with regards to the association between DHEA and different aspects of declarative, episodic and working memory, and sex and age differences in the cognitive effects of DHEA have been reported (de Menezes et al., 2016). In addition, there have been no studies, to our knowledge, examining the relationship between DHEA, brain structure, and working memory during development.

Yet, DHEA is likely to impact working memory in a developmentally sensitive manner, with possibly more prominent effects during adrenarche and middle childhood, when there is a steep rise in DHEA levels (Remer et al., 2005). Though levels of DHEA do not tend to show significant sex differences, some, though not all, studies suggest that sex could moderate the impact of adrenarche on brain function and mental health vulnerability, and the physical changes of adrenarche tend to occur at an earlier age in girls compared to boys (Byrne et al., 2017). DHEA may stimulate neurogenesis and protect against neuronal injury by opposing the neurotoxic effects of glucocorticoids in hippocampal as well as cortical structures (Jin et al., 2016; Karishma and Herbert, 2002; Kimonides et al., 1998; Nguyen et al., 2013b). These neurotoxic effects of glucocorticoids, which can affect both the cortex and hippocampus, may be especially detrimental during childhood and adolescence, as the brain experiences an accelerated increase in metabolic activity and cerebral perfusion throughout the pubertal maturation process (Campbell, 2011; Satterthwaite et al., 2014).

Cortical networks involved in cognitive control are known to regulate executive function, including working memory (Mazoyer et al., 2001). Cortico-hippocampal connections may also play a role in working memory, in particular for the maintenance of novel items in new contextual situations (Axmacher et al., 2007; Fuentemilla et al., 2010; Leszczynski, 2011; Poch et al., 2011; Ranganath and D'Esposito, 2001). More specifically, hippocampal-to-cortical afferents may be instrumental in the process of spatial encoding and spatial working memory (Spellman et al., 2015). In turn, DHEA may be involved in bolstering both cortical and hippocampal plasticity (Jin et al., 2016; Karishma and Herbert, 2002; Kimonides et al., 1998; Nguyen et al., 2013b), and DHEA levels or administration have been linked to improved attention and working memory in some, though not all, studies (do Vale et al., 2014; Nguyen et al., 2016; Ritsner et al., 2006; Strous et al., 2001; Wolf et al., 1998). Taken together, the current literature thus suggests that DHEA could significantly impact working memory during childhood and adolescence through an alteration in cortico-hippocampal networks.

Interestingly, there is accumulating evidence that these CNS effects could be directly related to DHEA itself rather than to other steroid hormones derived from its metabolism (Labrie et al., 2008; Labrie et al., 2005). In fact, major metabolites of DHEA in the hippocampus have been found to be essentially devoid of androgenic or estrogenic activity (Jellinck et al., 2005; Lu et al., 2003; Mo et al., 2004; Mo et al., 2006; Morfin and Starka, 2001), highlighting the critical role of DHEA itself in the survival of hippocampal neurons.

In summary, the current literature suggests that, during childhood and adolescence, DHEA may significantly affect cortical and hippocampal plasticity, in particular cortico-hippocampal structural covariance, and is likely to play a critical role in the development of working memory processes. Developmental coupling has previously been demonstrated between structural covariance and functional connectivity networks (Raznahan et al., 2011), reflecting the progressive integration of these networks between 5 and 18 years of age (Zielinski et al., 2010), and establishing structural covariance as a valid measure of developmental brain changes (Alexander-Bloch et al., 2013). Our investigation was based on data from 216 typically developing children and adolescents 6–22 years of age who were each followed longitudinally for a maximum of 4 years with repeated measurement of hormonal, cognitive and neuroimaging data every 2 years, in the context of the National Institutes of Health MRI Study of Normal Brain Development (NIHPD), a multi-site longitudinal study that aimed to provide a normative database to characterize healthy brain maturation. First, we tested for associations between DHEA and cortico-hippocampal structural covariance over time, looking at covariance between hippocampal volumes and cortical thickness across the whole brain. Second, we examined the relationship between DHEA-related cortico-hippocampal covariance and two tests of working memory: (1) a laboratory, clinical performance test of spatial working memory (Cambridge Neuropsychological Test Automated Battery [CANTAB] (Luciana, 2003); and (2) a parent-rated measure of everyday working memory exhibited by the child/adolescent in real-world situations (Behavior Rating Inventory of Executive Function [BRIEF] (Gioia et al., 2002b)). Third, we tested whether the relationship between DHEA and working memory was mediated by cortico-hippocampal structural covariance. Finally, because DHEA previously showed age-related associations with cortical thickness (Nguyen et al., 2013b), and because sex may moderate both the impact of DHEA on brain structure and working memory (Byrne et al., 2017), we tested for age and sex interaction effects in all of the above relationships. We hypothesized that DHEA levels would be associated with cortico-hippocampal structural covariance, particularly in regions involved in cognitive control. In turn, we expected these cortico-hippocampal networks to mediate the relationship between DHEA and working memory, and for that effect to be moderated by age and sex.

2. Methods and materials

2.1. Sampling and recruitment

Participants were recruited across the United States with a population-based sampling method seeking to achieve a representative sample in terms of income level, race and ethnicity (Evans, 2006). All experiments on human participants were conducted in accordance with the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written parental consent, as well as assent of the participants (or consent, if $> = 18$ years old). Participants underwent repeated magnetic resonance brain imaging (MRI) every 2 years. For the subjects included in this study, age at first visit was between 6 and 18 years old, with each child then followed longitudinally for a maximum of 3 visits, over the course of 4 years (i.e. full age span 6–22 years, one to three visits per child). The sample was limited to