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The developmental relationship between DHEA and visual attention is mediated by structural plasticity of cortico-amygdalar networks

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ABSTRACT

Humans and the great apes are the only species demonstrated to exhibit adrenarche, a key developmental event leading to increased production of dehydroepiandrosterone (DHEA), suggesting that this hormone may play an important evolutionary role. Similarly, visual attention networks have been shown to evolve in a human-specific manner, with some anatomical connections and elements of cortical organization exclusive to our species. Existing studies of human brain development support the notion that DHEA shows significant uptake in cortical structures and the amygdala, and as such, could be involved in the bottom-up regulation of visual attention. Here we examined associations between DHEA, structural covariance of the amygdala with whole-brain cortical thickness, and tests of visual attention, in a longitudinal sample of typically developing children and adolescents 6–22 years of age. We found that DHEA predicted covariance between amygdalar volume and the left occipital pole, right somatosensory parietal cortex and right anterior cingulate cortex. Amygdala-occipital covariance predicted visual awareness; amygdala-parietal covariance predicted visuo-motor dexterity and processing speed; amygdala-prefrontal covariance predicted global attentional impairment. Further, effects of DHEA were above and beyond those of age and sex, as well as distinct from those of pubertal stage, estradiol and testosterone. These findings support the notion that DHEA may play a unique role in shaping amygdala-dependent cortical plasticity and in regulating 'bottom-up' visual attention processes from childhood to young adulthood.

1. Introduction

Humans and the great apes are the only species demonstrated to exhibit adrenarche, a key developmental event leading to increased production of dehydroepiandrosterone (DHEA) (Remer et al., 2005), suggesting that this hormone may play an important evolutionary role in brain development. DHEA levels represent the most abundant steroid hormone in production across the lifespan, maintained at high levels from middle childhood until the third decade of life (Adams, 1985).

Evidence at the molecular level has confirmed the important role of DHEA in enhancing neuronal and glial plasticity, through a variety of peripheral and central mechanisms (Compagnone and Mellon, 2000; Li et al., 2008; Maninger et al., 2009). Of these, the most relevant to human development may be the anti-glucocorticoid effects of DHEA, which play an important role in metabolically active brain regions. Through these anti-

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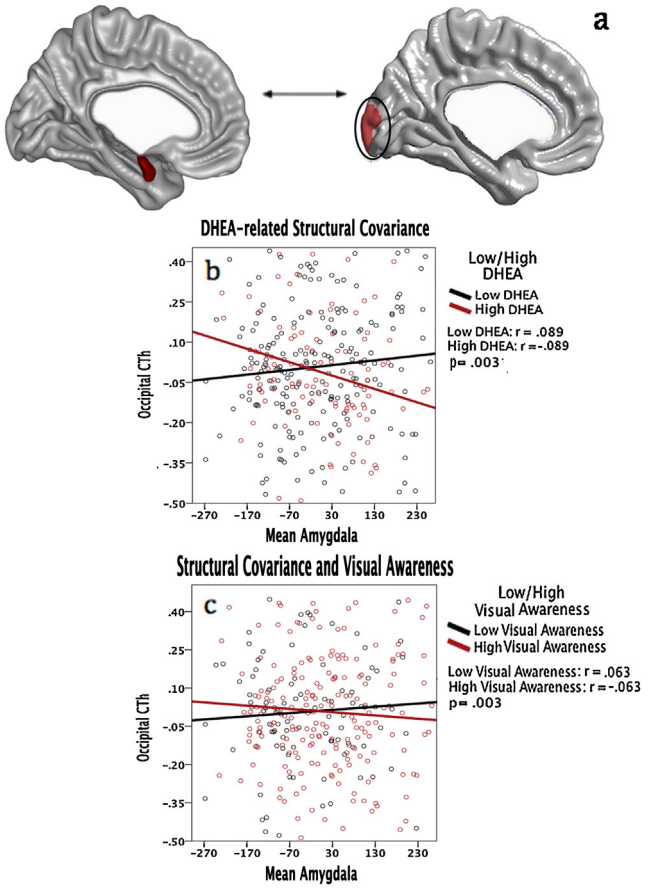

Fig. 1. DHEA-related amygdala-occipital covariance and relationship with visual awareness. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

This figure shows cortico-amygdalar covariance related to DHEA levels and to visual awareness (Fig. 1a–c). Higher DHEA levels are associated with a negative covariance between amygdalar volume and cortical thickness of the left occipital pole (Fig. 1b). In turn, negative covariance between these regions is associated with higher scores on a test of visual awareness (Fig 1c).

Note that standardized residuals (accounting for the effects of age, sex, handedness, scanner, and total brain volume in all analyses, as well as collection time for DHEA-related analyses) were used for cortical thickness values on the Y axes of Fig. 1b and c. Occipital CTh stands for cortical thickness of the occipital region displayed in Fig. 1a.

DHEA and cognitive scores were split into high and low groups for the purposes of visualization, based on the values at which cortico-amygdalar covariance shifted from positive to negative. Both variables were included as continuous variables in all analyses.

glucocorticoid effects, DHEA preserves anabolic potential by increasing reserves in mitochondrial energy (Campbell, 2011). Because release of neurotransmitters during neuronal firing is thought to rely directly on mitochondrial energy, these effects of DHEA represent a direct mechanism through which it could alter activity-dependent synaptogenesis (Vos et al., 2010).

Similar to molecular studies, 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 (Herting et al., 2015; Nguyen et al., 2013b). In addition, DHEA administration has been specifically linked to optimal performance on tests of attention and executive control, with paradoxical detrimental effects on declarative memory (Sripada et al., 2013; Strous et al., 2001; Wolf et al., 1998).

Yet, beyond cortical structures, DHEA also shows significant uptake in the amygdala (Regelson and Kalimi, 1994; Sripada et al., 2013), a structure traditionally thought to be the affective center of the brain (Sah et al., 2003). Interestingly, there is accumulating evidence to suggest that the amygdala is also centrally involved in the 'bottom-up' regulation of primary (i.e. perceptual salience) and secondary (i.e. goal-directed) attentional processes (Pessoa, 2008). The relationship between primary and secondary attentional processes may be facilitated by amygdala-dependent cortical plasticity, a process through which activation of the amygdala induces plasticity in sensory cortical regions in a modality-specific manner (Phelps and LeDoux, 2005). These structural effects of the amygdala are supported by previous findings of anatomical covariance between the amygdala and bilateral dorsolateral and dorsomedial prefrontal, inferior parietal, as well as bilateral orbital and ventromedial prefrontal cortices (Albaugh et al., 2013).

'Bottom up' cortical-subcortical systems have been shown to mature earlier than 'top-down' systems during adolescence (Casey and Jones, 2010). Of particular interest is the existence of an afferent subcortical visual pathway directly connected to the amygdala, with efferent projections from the amygdala to sensory cortical regions subsequently involved in 'bottom-up' regulation of visual awareness (Morris et al., 2001; Pasley et al., 2004; Pegna et al., 2005; Vuilleumier et al., 2003; Williams et al., 2004). Amygdala-dependent regulation of visual awareness may extend to the control of simple motor and more complex behaviors in response to visual stimuli (Pessoa, 2008; Phelps and LeDoux, 2005). These 'bottom-up' visual attention networks emerge during middle childhood, coinciding with increased DHEA production (Campbell, 2011). Similar to the unique presence of adrenarche in humans and the great apes, visual attention networks have been shown to evolve in a human-specific manner, with some anatomical connections and elements of cortical organization exclusive to our species (Patel et al., 2015; Preuss and Coleman, 2002). Taken together, the timing of the abrupt rise of DHEA, its effects on cortico-amygdalar structures and cognitive function, and its importance in human development all point toward a potentially unique role in the 'bottom-up' regulation of amygdalar-dependent cortical plasticity and visual attention in humans.

In sum, DHEA may regulate the relationship, or covariance, between amygdalar and cortical structures. DHEA-related structural covariance may in turn parallel the development of functional networks (Raznahan et al., 2011), leading to altered performance on measures of visual attention. To test these hypotheses, we examined associations between DHEA, structural covariance of the amygdala with whole-brain cortical thickness, and tests of visual attention, in a longitudinal sample of typically developing children and adolescents 6–22 years of age.

2. Methods and materials

2.1. Sampling and recruitment

The National Institutes of Health (NIH) MRI Study of Normal Brain Development is a multi-site project that aimed to provide a normative database to characterize healthy brain maturation. Subjects 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 subjects 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 subjects (or consent, if > = 18 years old). Subjects underwent repeated magnetic resonance brain imaging (MRI) every 2 years, with a maximum of 3 scans over 4 years. The sample was limited to developmentally healthy children with rigorous exclusion criteria, described in detail elsewhere (Evans,