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# The effects of age, sex, and hormones on emotional conflict-related brain response during adolescence

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ABSTRACT

While cognitive and emotional systems both undergo development during adolescence, few studies have explored top-down inhibitory control brain activity in the context of affective processing, critical to informing adolescent psychopathology. In this study, we used functional magnetic resonance imaging to examine brain response during an Emotional Conflict (EmC) Task across 10–15-year-old youth. During the EmC Task, participants indicated the emotion of facial expressions, while disregarding emotion-congruent and incongruent words printed across the faces. We examined the relationships of age, sex, and gonadal hormones with brain activity on Incongruent vs. Congruent trials. Age was negatively associated with middle frontal gyrus activity, controlling for performance and movement confounds. Sex differences were present in occipital and parietal cortices, and were driven by activation in females, and deactivation in males to Congruent trials. Testosterone was negatively related with frontal and striatal brain response in males, and cerebellar and precuneus response in females. Estradiol was negatively related with fronto-cerebellar, cingulate, and precuneus brain activity in males, and positively related with occipital response in females. To our knowledge, this is the first study reporting the effects of age, sex, and sex steroids during an emotion–cognition task in adolescents. Further research is needed to examine longitudinal development of emotion–cognition interactions and deviations in psychiatric disorders in adolescence.

## 1. Introduction

Adolescence represents a period of emotional, cognitive, pubertal, psychological, and social maturation. Despite improvements in cognitive and emotional functioning (Durand, Gallay, Seigneuric, Robichon, & Baudouin, 2007; Luna et al., 2001; Tottenham, Hare, & Casey, 2011), this developmental stage has often been characterized as a time of increased vulnerability for the emergence of psychopathology (Dahl & Gunnar, 2009; Ernst & Korelitz, 2009). One prominent theory for this vulnerability is heightened emotional reactivity during adolescence in the face of less mature cognitive control (Dahl, 2004). As a result, neuroimaging studies of adolescent brain development have aimed to understand the neurobiological underpinnings of adolescent emotional and cognitive maturation. Magnetic resonance imaging (MRI) has revealed changes in brain maturation over the course of adolescence, suggesting that brain regions subserving affective and cognitive functions mature at different rates (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). In addition to regionally specific developmental timecourses for subcortical and cortical brain structures (Dennison et al., 2013; Giedd et al., 1999; Gogtay et al., 2004; Mills et al., 2014; Ostby et al., 2009; Sowell, Thompson, Tessner, & Toga, 2001; Sowell et al., 1999, 2002), it is proposed that the maturation of affective brain regions occurs prior to that of cognitive control regions, resulting in an imbalance between "hot" and "cold" neurocognitive processes during adolescence (Dahl, 2001, 2004; Ladouceur, 2012; Mueller, 2011), and a recent longitudinal study supports this theory (Mills et al., 2014). Thus, the earlier maturational trajectory of subcortical brain regions that subserve bottom-up emotional processing relative to the later trajectory of cortical regions involved in top-down higher order cognitive control may explain some of the vulnerability for the emergence of psychiatric disorders during adolescence.

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However, recent reviews present alternative explanations for heightened emotionality and immature cognitive control during adolescence (Crone & Dahl, 2012; Pfeifer & Allen, 2012). These authors point to the mixed evidence for immaturity in the frontal lobe, and suggest that other important factors, such as motivation, social and affective context, training, capacity for learning, flexibility, and task-related factors may better explain changes in behavior during adolescence (Crone & Dahl, 2012; Pfeifer & Allen, 2012). For example, adolescence coincides with a time of increased social and peer engagement, which while evolutionarily adaptive (Steinberg, 2008), has been linked with increased risk-taking and affective disorders, thought to be influenced by pubertal maturation (Forbes & Dahl, 2010; Hamilton, Hamlat, Stange, Abramson, & Alloy, 2014; Smith, Chein, & Steinberg, 2013). Pubertal stage impacts emotional responsivity and associated brain activity (Forbes, Phillips, Silk, Ryan, & Dahl, 2011; Moore et al., 2012), such that limbic and visual cortical processing of emotional faces are associated with puberty at younger ages, while prefrontal cortical processing of affective displays is correlated with puberty at older ages (Moore et al., 2012). While increased prefrontal cortex engagement during emotional face processing may be present in older adolescents, higher levels of testosterone have been shown to reduce the coupling between prefrontal cortex and the amygdala (Spielberg et al., 2014; Volman, Toni, Verhagen, & Roelofs, 2011). These findings emphasize the importance of studying adolescent cognition within emotional contexts.

While emotional processing (e.g. brain activity in response to emotional faces) and cognitive control (e.g. brain activity during response inhibition) are often studied separately in adolescent neuroimaging studies (Adleman et al., 2002; Guyer et al., 2008; Herba, Landau, Russell, Ecker, & Phillips, 2006; Luna et al., 2001; Marsh et al., 2006; Rubia, Smith, Taylor, & Brammer, 2007; Rubia et al., 2006; Tamm, Menon, & Reiss, 2002), top-down executive control and affective processing are often not isolated processes in the environment. Functional magnetic resonance imaging (fMRI) studies of inhibitory control in adolescents show age-related changes in behavior, as well as both greater and less brain activity with age (Luna et al., 2001; Marsh et al., 2006; Rubia et al., 2006; Tamm et al., 2002; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Developmental changes in behavior and brain response have also been documented in emotional processing studies, many of which suggest increases in emotion recognition abilities across development and relatively higher emotion-related brain activity during adolescence compared with other periods of life (Durand et al., 2007; Gao & Maurer, 2010; Guyer et al., 2008; Herba et al., 2006; Pfeifer et al., 2011). However, few studies of emotion–cognition interactions during development are present in the adolescent literature. Existing studies have examined emotional processing effects on inhibitory control during go–nogo tasks (Hare et al., 2008; Schel & Crone, 2013; Somerville, Hare, & Casey, 2011; Tottenham et al., 2011), cognitive interference during an emotional Stroop task (Mincic, 2010), and the effects of emotional valence on interference during a working memory task (Ladouceur et al., 2005). With respect to emotion–cognition interactions, only one of these studies used fMRI to examine developmental effects and found a negative association between age and inferior frontal gyrus activity during response inhibition (Somerville et al., 2011). Due to limited knowledge of how these different neural networks interact during adolescence, further research on emotion–cognition interactions is needed to improve our understanding of the maturational changes occurring simultaneously within these systems. By understanding how these systems are engaged during typical adolescent brain development, researchers will be better able to interpret brain activity observed in internalizing and externalizing disorders that emerge during adolescence.

Another important factor to consider during development is sex differences, which exist both structurally (see Giedd, Raznahan, Mills, and Lenroot (2012) for review) and functionally (Rubia, Hyde, Halari, Giampietro, & Smith, 2010; Rubia et al., 2013; Schneider et al., 2011; Schweinsburg, Nagel, & Tapert, 2005) in the adolescent brain. Functional differences between the sexes have been observed during attention allocation (Rubia et al., 2010), inhibitory control (Christakou et al., 2009; Rubia et al., 2013), emotional processing in the amygdala (Schneider et al., 2011), and spatial working memory (Alarcon, Cservenka, Fair, & Nagel, 2014; Schweinsburg et al., 2005) in adolescents. Specifically, during inhibitory control, left hemispheric fronto-striatal activity is greater in girls, while parietal activity is greater in boys, and age-by-sex interactions in these same regions are believed to reflect sex-specific changes in functional maturation (Christakou et al., 2009; Rubia et al., 2013). Not only are brain volume and activity differences present between the sexes, but the prevalence of psychiatric disorders also varies between males and females, such that externalizing disorders are more often seen in males, while internalizing disorders are more prevalent in females (Earls, 1987). Understanding sex differences in healthy adolescent brain response during emotion–cognition interactions may help explain sex-specific rates of occurrence of these disorders.

In addition to age-related and sex-specific changes in brain maturation, pubertal status has also been shown to impact brain structure (Blanton et al., 2012; Giedd et al., 2006; Goddings et al., 2014) and function (Forbes et al., 2011; Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012; Klapwijk et al., 2013; Moore et al., 2012). Functional studies suggest that stage of pubertal development is associated with changes in socio-affective response and connectivity during adolescence (Forbes et al., 2011; Goddings et al., 2012; Klapwijk et al., 2013; Moore et al., 2012). For example, pre-/early pubertal adolescents show relatively heightened amygdalar and ventrolateral prefrontal cortex activity to emotional faces, compared with mid/late-pubertal adolescents (Forbes et al., 2011). During this time, they also show increases in amygdalar, hippocampal, and temporal lobe activity, and activation in prefrontal areas, previously unobserved in childhood (Moore et al., 2012). Furthermore, these studies suggest that underlying hormonal changes may, in part, explain why pubertal status accounts for some of the variance in brain development. Structural MRI (Bramen et al., 2011, 2012; Herting et al., 2014; Peper et al., 2009), diffusion tensor imaging (Herting, Maxwell, Irvine, & Nagel, 2012), and fMRI (Goddings et al., 2012; Klapwijk et al., 2013; Op de Macks et al., 2011) studies have found relationships between sex steroids and brain anatomy and activity, respectively, in healthy adolescent samples. Pubertal maturation may be particularly relevant to the development of brain systems underlying social and reward-related processing during adolescence. For example, testosterone and estradiol are positively associated with social vs. basic emotional processing brain activity (Goddings et al., 2012), with estradiol relating to greater connectivity among social brain processing regions in girls (Klapwijk et al., 2013). These findings could underlie adolescent movement toward emotionally salient peer relationships. Further, reward-related striatal response is positively associated with testosterone in both males and females (Op de Macks et al., 2011), further supporting hormonal roles in affectively and/or motivationally driven neural systems. Thus, studies examining hormone levels and brain activity in healthy adolescents may help inform future studies of atypical neurodevelopment, where hormone levels or their influence on brain structure and/or functioning may be altered.

To expand upon existing literature and examine the impact of the aforementioned variables, we implemented a modified Emotional Conflict (EmC) Task (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006) in a typically developing adolescent population.