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Sex differences in the neural substrates of spatial working memory during adolescence are not mediated by endogenous testosterone

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ABSTRACT

Adolescence is a developmental period characterized by notable changes in behavior, physical attributes, and an increase in endogenous sex steroid hormones, which may impact cognitive functioning. Moreover, sex differences in brain structure are present, leading to differences in neural function and cognition. Here, we examine sex differences in performance and blood oxygen level-dependent (BOLD) activation in a sample of adolescents during a spatial working memory (SWM) task. We also examine whether endogenous testosterone levels mediate differential brain activity between the sexes. Adolescents between ages 10 and 16 years completed a SWM functional magnetic resonance imaging (fMRI) task, and serum hormone levels were assessed within seven days of scanning. While there were no sex differences in task performance (accuracy and reaction time), differences in BOLD response between girls and boys emerged, with girls deactivating brain regions in the default mode network and boys showing increased response in SWM-related brain regions of the frontal cortex. These results suggest that adolescent boys and girls adopted distinct neural strategies, while maintaining spatial cognitive strategies that facilitated comparable cognitive performance of a SWM task. A nonparametric bootstrapping procedure revealed that testosterone did not mediate sex-specific brain activity, suggesting that sex differences in BOLD activation during SWM may be better explained by other factors, such as early organizational effects of sex steroids or environmental influences. Elucidating sex differences in neural function and the influence of gonadal hormones can serve as a basis of comparison for understanding sexually dimorphic neurodevelopment and inform sex-specific psychopathology that emerges in adolescence.

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1. Introduction

Adolescence is a developmental period marked by a reactivation of sex hormones and reorganization of brain structure and function. As such, it affords a unique window into an important stage of neural and behavioral change. Research on anatomical development of the human brain suggests that frontal and parietal cortical maturation extends well past adolescence (Giedd 2004; Gogtay et al., 2004; Koolschijn et al., 2014) and occurs at different rates for males and females, with girls peaking approximately two years earlier (Lenroot et al., 2007; Bramen et al., 2012). These regions play a critical role in executive functioning at various stages of development (Casey et al., 1995; Klingberg et al., 2002; Kwon et al., 2002). Along the same lines, brain regions underlying spatial working memory (SWM) abilities mature throughout adolescence (Klingberg et al., 2002; Kwon et al., 2002; Schweinsburg et al., 2005). Despite our knowledge of neurodevelopmental sex differences during the adolescent years, differences in the neural mechanisms underlying SWM function in adolescent boys and girls and potential contributing factors, such as gonadal sex hormones, have been largely unexplored. Previous studies have reported positive associations between testosterone and gray and white matter volumes in adolescent boys (Peper et al., 2009; Perrin et al., 2008), and regional effects of androgen receptor function have been related to cortical thinning of frontal brain areas (Raznahan et al., 2010), highlighting the relevance of testosterone on brain maturation. Gaining a broader insight into the mechanisms that help differentiate adolescent brains from other stages of development and whether these differences are meaningfully explained by testosterone can further the understanding of healthy neurodevelopment through which deviations caused by psychopathology can be compared.

1.1. *Fronto-parietal neurodevelopment underlies maturation of working memory*

Working memory is defined as the active process of maintaining and manipulating information in the mind (Baddeley, 1992). In the context of executive functions, working memory is only one type of higher order cognitive process, and often overlaps with other processes like attention and inhibition. This overlap is tightly linked to underlying cortical pathways and neurotransmitter innervations between the prefrontal and posterior parietal cortices that facilitate distributed processing (Katsuki and Constantinidis, 2012). Research examining anatomical development of the brain has shown that cortical development begins with primary sensorimotor cortices and frontal and occipital poles, and ends with cortical development of parietal and then frontal lobes (Gogtay et al., 2004). Moreover, development of the cortex coincides with a progressive increase in cognitive abilities that require engagement of frontal and parietal brain regions (Kwon et al., 2002).

In the context of functional magnetic resonance imaging (fMRI) research, SWM has been studied most extensively in healthy adults and to a lesser degree in children and adolescents. Studies consistently show that adults have activation of premotor, lateral prefrontal and posterior parietal cortices during SWM tasks (Owen, 1997; Owen et al., 2005; Fletcher and Henson, 2001; Rypma et al., 1999). Similar patterns of brain activation during SWM have been shown in younger populations (Thomas et al., 1999; Thomason et al., 2009), with children having more widespread activation (Geier et al., 2009) and bilateral recruitment of prefrontal and parietal regions relative to adults (Klingberg et al., 2002; Kwon et al., 2002; Schweinsburg et al., 2005). During adolescence, activation of frontal and parietal brain regions increases relative to childhood, while the transition into adulthood involves specialized recruitment of prefrontal and posterior parietal brain areas (Scherf et al., 2006).

1.2. *Sex differences in spatial cognition and effects of gonadal sex steroids*

Some evidence in human adults suggests that visuospatial functioning is superior in males relative to females (Voyer et al., 1995; Vecchi and Girelli, 1998; Astur et al., 1998; Rizk-Jackson et al., 2006); however, the few adult studies that have examined behavioral sex differences in SWM directly have mixed results (Janowsky et al., 2000; Minor and Park, 1999; Duff and Hampson, 2001; Lejbak et al., 2011). A few other studies have examined sex differences in brain response during other types of working memory, such as verbal or object working memory, but have also yielded mixed results (Schmidt et al., 2009; Bell et al., 2006; Frings et al., 2006). Only one study, by Schweinsburg and colleagues, has examined sex differences in brain activation during SWM in healthy adolescents, and they reported sex differences in blood oxygen level-dependent (BOLD) activation that included frontopolar regions in brains of a healthy adolescent sample, with boys showing increased BOLD response, in comparison to girls (Schweinsburg et al., 2005). As there were no sex differences in performance, differences in BOLD response could not be explained by task behavior. Given the significance of adolescence for the development of executive functions, it is important to examine sex-dependent effects of SWM BOLD activation in this context, and whether other sex-specific variables, such as testosterone, may impact patterns of neural activity.

Testosterone is a potential factor mediating adolescent sex differences in SWM because of its dramatic increase during adolescence, especially in males, and its purported role in spatial cognition (Moffat and Hampson, 1996; Janowsky et al., 1994; Hawley et al., 2013). Furthermore, increases in circulating testosterone are associated with brain regions (Perrin et al., 2008; Raznahan et al., 2010; Witte et al., 2010; Peper et al., 2011; Neufang et al., 2009) that impact cognitive functioning (Mueller et al., 2011) and differentiate adolescence from other developmental periods. One fMRI study measuring the relationship between sex hormone levels and brain response during mental rotation (a visuospatial task) found a positive association between testosterone levels and activation of inferior frontal gyrus, ventromedial prefrontal cortex, inferior parietal lobe, and left supramarginal gyrus in both men and women (Schoning et al., 2007). This study demonstrated that testosterone can impact degree of activation in the brain in response to a cognitive task with