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# The effects of puberty on white matter development in boys

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ABSTRACT

Neuroimaging studies demonstrate considerable changes in white matter volume and microstructure during adolescence. Most studies have focused on age-related effects, whilst puberty-related changes are not well understood. Using diffusion tensor imaging and tract-based spatial statistics, we investigated the effects of pubertal status on white matter mean diffusivity (MD) and fractional anisotropy (FA) in 61 males aged 12.7–16.0 years. Participants were grouped into early-mid puberty (≤Tanner Stage 3 in pubic hair and gonadal development; $n = 22$) and late-post puberty (≥Tanner Stage 4 in pubic hair or gonadal development; $n = 39$). Salivary levels of pubertal hormones (testosterone, DHEA and oestradiol) were also measured. Pubertal stage was significantly related to MD in diverse white matter regions. No relationship was observed between pubertal status and FA. Regression modelling of MD in the significant regions demonstrated that an interaction model incorporating puberty, age and puberty × age best explained our findings. In addition, testosterone was correlated with MD in these pubertally significant regions. No relationship was observed between oestradiol or DHEA and MD. In conclusion, pubertal status was significantly related to MD, but not FA, and this relationship cannot be explained by changes in chronological age alone.



## 1. Introduction

Cross-sectional and longitudinal structural magnetic resonance imaging (MRI) studies have demonstrated that the human brain undergoes significant development during adolescence (Gogtay et al., 2004; Sowell et al., 2004; Lenroot et al., 2007; Shaw et al., 2008; Giorgio et al., 2010; Raznahan et al., 2011; Ball et al., 2012). These studies have shown that, generally, grey matter decreases in volume during adolescence, with regional variations in precise timing, while white matter volume increases across the brain. The changes occurring at a cellular level that lead to these volume increases are unclear, since neuroimaging lacks the resolution to study this directly. White matter is composed primarily of axons, many of which are myelinated, and associated vasculature and glia. The increases in white matter in adolescence have been proposed to reflect increased axonal calibre within fibre bundles (Paus, 2010) and/or myelination, which in humans continues well into the second and even the third decade of life (Miller et al., 2012).

Diffusion tensor imaging (DTI) provides in vivo quantitative information about white matter microstructure rather than just assessing volumetric changes in white

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matter (Basser and Pierpaoli, 1996; Le Bihan et al., 2001). Two commonly considered DTI measures are mean diffusivity (MD) and fractional anisotropy (FA) (Basser et al., 1994). MD is a measure of the overall magnitude of water diffusion in any direction, and is sensitive to the number of cells and their processes in a region. In a tight bundle of axons, in which diffusion is restricted due to the large myelin lipids, water diffusion is restricted and MD is low. If the number of cells or cell components (for example myelin, axons or glia) in the region increases, then diffusion will be further restricted and MD will decrease. FA provides information regarding the directionality of diffusion, and represents the extent to which diffusion occurs preferentially in one direction; this measure increases as the extent of axonal myelination increases, or as axons become more coherently organised in a uniform direction (Beaulieu, 2002).

Studies exploring age effects on diffusion indices have consistently identified increases in FA and decreases with MD during adolescence (Klingberg et al., 1999; Morriss et al., 1999; Mukherjee et al., 2001; Schmithorst et al., 2002; Schneider et al., 2004; Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Snook et al., 2005; Ashtari et al., 2007; Bonekamp et al., 2007; Eluvathingal et al., 2007; Schneiderman et al., 2007; Giorgio et al., 2008; Lebel et al., 2008; Qiu et al., 2008; Tamnes et al., 2010; Bava et al., 2010; Lebel and Beaulieu, 2011; Simmonds et al., 2013). FA increases are generally driven more by reductions in radial diffusion (RD) (in the perpendicular plane to predominant diffusion direction) than by changes in axial diffusion (AD) (in the plane parallel to predominant diffusion direction) (Giorgio et al., 2008; Lebel et al., 2008), although some studies have reported a decrease in both modalities (Eluvathingal et al., 2007).

## 2. Pubertal effects on white matter development

To date, almost all developmental MRI studies of white matter development have investigated the effects of chronological age on brain structure, without accounting for the potential impact of other concurrent physiological processes that occur during adolescence (Ladouceur et al., 2012). Chronological age can be considered as a composite measure of development that incorporates a multitude of different social, physiological and psychological exposures. It has been hypothesised that the brain development observed in adolescence is significantly related to the hormonal influences that control the onset of and progression through puberty (Giedd et al., 1999; Lenroot et al., 2007; Peper et al., 2011; Sowell et al., 2002). Puberty is the process by which sexual maturity and reproductive capacity are achieved. It encompasses two distinct hormonal processes: adrenarche, the activation of the zona reticularis of the adrenal gland, and gonadarche, the activation of the gonads. These two processes trigger a rise in the production of pubertal hormones, particularly sex steroid hormones such as testosterone, dehydroepiandrosterone (DHEA) and oestradiol, resulting in physical changes such as linear and organ system growth, development of the gonads and emergence of secondary sexual characteristics, as well as changes in body proportion and facial bone structure (Verdonck et al., 1999; Lee and Houk, 2006; Meindl et al., 2012). It has been proposed that puberty may mediate changes in brain structure and function (Patton and Viner, 2007; Steinberg, 2007; Paus et al., 2008; Forbes and Dahl, 2010), and that differences in the developmental trajectories of white matter development between the sexes during adolescence, with more protracted and extensive increases in white matter volume in boys compared with girls, may reflect the different hormonal exposures and differences in pubertal timing observed between males and females (Lenroot et al., 2007; Blakemore et al., 2010).

Only two studies have investigated whether pubertal factors also influence white matter microstructure in adolescence, in addition to effects of age. The first study looked at RD in white matter tracts in males and females aged 8–28 years ($n = 114$, 63 females), and explored whether pubertal effects were present in tract regions of interest that showed significant age effects (Asato et al., 2010). Several association and projection tracts across the brain demonstrated continued immaturity (that is, a relatively high RD) in early and mid-puberty, suggesting that pubertal changes and white matter maturation may be more tightly coupled than previously thought. A second study ($n = 77$, 39 female; ages 10–16 years) reported increased FA in boys in cortico-spinal, long-range association and cortico-subcortical white matter, and reduced MD in frontal and temporal white matter compared with girls, and found that pubertal hormones such as testosterone explained variation in microstructure within some white matter regions (Herting et al., 2012). Other supporting evidence for pubertal effects on white matter in humans comes from studies looking at white matter volumetric and density changes. It has been shown that white matter density in frontal, parietal and occipital lobes increases with pubertal maturation in boys only, but decreases in cortico-spinal tracts (Perrin et al., 2009).

There is also evidence from animal studies concerning the role of puberty and pubertal hormones in brain development. These studies, mostly conducted in rodents, have provided evidence that adolescence is the second of two windows of sensitivity of the brain to sex steroids such as testosterone (Schulz and Sisk, 2006; Juraska et al., 2013). This framework, referred to as the 'organisational-activational hypothesis', involves an initial transient rise in testosterone during prenatal or early postnatal development which masculinises neural circuits in males, the absence of which in females results in development of a feminine phenotype. Later on, during puberty, testosterone and oestradiol are produced following gonadal maturation, and act upon sexually dimorphic neural circuits to facilitate sexually specific behaviours (Schulz et al., 2009; De Lorme et al., 2012). Of note, studies actively manipulating hormone levels are limited to animal models, which may not adequately capture the full complexity of human hormonal changes in childhood and adolescence. Puberty in humans incorporates not just gonadarche (activation of the gonads at the end of childhood) but also adrenarche (activation of the adrenal gland to produce androgens), which is not evident in rodents, and which may also relate to brain maturation (Nguyen et al., 2013).