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Review

# White matter development in adolescence: The influence of puberty and implications for affective disorders

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ABSTRACT

There have been rapid advances in understanding a broad range of changes in brain structure and function during adolescence, and a growing interest in identifying which of these neurodevelopmental changes are directly linked with pubertal maturation—at least in part because of their potential to provide insights into the numerous emotional and behavioral health problems that emerge during this developmental period. This review focuses on what is known about the influence of puberty on white matter development in adolescence. We focus on white matter because of its role in providing the structural architectural organization of the brain and as a structural correlate of communication within complex neural systems. We begin with a review of studies that report sex differences or sex by age interactions in white matter development as these findings can provide, although indirectly, information relevant to puberty-related changes. Studies are also critically reviewed based on methodological procedures used to assess pubertal maturation and relations with white matter changes. Findings are discussed in light of their implications for the development of neural systems underlying the regulation of emotion and behavior and how alterations in the development of these systems may mediate risk for affective disorders in vulnerable adolescents.



**Contents**



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## 1. Introduction

The onset of adolescence, specifically the emergence of puberty, represents a key developmental window for understanding physical, emotional, cognitive, and social changes, which may mediate the emergence of a broad range of behavioral and emotional health problems during adolescent development (Dahl & Spear, 2004; Steinberg, 2005). The onset of puberty in early adolescence initiates a cascade of dramatic physical, psychological, and social changes (Schulz et al., 2009; Spear, 2010). It is a time during which there are substantial increases in hormonal levels as well as physical growth and alterations in physical appearance (e.g., emergence of secondary sexual characteristics and changes in body proportion, as well as sexually dimorphic facial appearance including alterations in facial bone structure, facial hair, and fullness of lips). Amidst these changes in early adolescence arise sharp increases in the rate of problems associated with the regulation of emotion and behavior, including increases in risk-taking behaviors, sensation-seeking, experimenting with alcohol and substance use, the number of accidents, suicide, as well as the prevalence of affective disorders (Dahl & Spear, 2004; Centers for Disease Control and Prevention, 2009). Such changes in the regulation of emotion and behavior may be mediated by puberty-specific changes in brain development. Indeed, a growing number of neuroimaging studies demonstrate that adolescence involves ongoing changes in brain structure and function (Galvan, 2011; Giedd et al., 1999; Lenroot & Giedd, 2006; Luna et al., 2011; Peper et al., 2011).

A central component to pubertal maturation is the sharp increase in reproductive hormones, which has been shown in animal work to be responsible for the development of secondary sexual characteristics influencing the physical appearance and function but also for key aspects of neural function through binding to testosterone and estrogen receptors in specific neural regions (Schulz et al., 2009; Spear, 2010). Research studies, for instance, have used rodent models to demonstrate that the effects of exposure to reproductive hormones during adolescence persist after hormones have been removed, suggesting that the onset of puberty and secretion of puberty-related hormones may have a significant impact on brain development (Schulz & Sisk, 2006; Sisk & Foster, 2004). In addition, evidence from animal studies suggest that gonadal steroids influence brain development in various ways such as neurogenesis and neurite outgrowth (McEwen & Alves, 1999), axonal myelination (Yates & Juraska, 2008), and growth of astrocyte processes in white matter (Chowen et al., 2000). Some studies have documented high densities of steroid hormone receptors in medial temporal regions (Sarkey et al., 2008), including amygdala and hippocampus, as well as the prefrontal cortex (Simerly et al., 1990). Furthermore, administration of androgens to pubertal rats yielded increased neuronal spine density within the amygdala and hippocampus (Cunningham et al., 2007). Thus, puberty would appear to have specific influences on several developing neural systems, including corticolimbic systems implicated in emotion regulation. In humans, it has been hypothesized that puberty constitutes a sensitive period for gonadal steroids to organize the brain (Romeo, 2003; Schulz et al., 2009). Yet, relatively little is known about how puberty specifically influences adolescent brain development (see Blakemore et al., 2010; Forbes & Dahl, 2010).

Recently, a number of research studies have emerged providing some evidence about the relation between puberty and white matter development. White matter consists of myelin-coated axons that are bundled into tracts concentrated mostly in the inner-portion of the brain. These tracts serve to facilitate communication between neural regions creating neural networks (Paus, 2010). Some of these neural networks implicate cortico-cortical as well as cortico-subcortical connections that subserve cognitive and affective functions. In order to better understand the developmental mechanisms underlying changes in neural systems implicated in the regulation of emotion and behavior in adolescence, we therefore focused this review on the specific influence of puberty on white matter development as determined through structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) techniques.

We are aware of reviews that have examined brain development during adolescence (e.g., Blakemore et al., 2010; Casey et al., 2010), including reviews focusing on sex differences (sexual dimorphism) (Lenroot & Giedd, 2010), sex steroids (Peper et al., 2011), puberty (Giedd et al., 2006) and white matter development in adolescence (Paus, 2010; Schmithorst & Yuan, 2010). In contrast to prior reviews on adolescent brain development, our review focuses on recent findings documenting *puberty-specific changes in white matter development*. It also includes a critical review of methodological procedures used to assess pubertal maturation, discussing, for instance, how studies are able to disentangle age effects from pubertal maturation since age and puberty are closely correlated with each other (and chronological age is measured with a much greater precision than categories for pubertal stage) (Shirtcliff et al., 2009; Spear, 2010). To begin, we provide an overview of the hormonal and physical changes associated with puberty

and how pubertal maturation is commonly assessed (for a more detailed review, see Blakemore et al., 2010; Dorn et al., 2006; Shirtcliff et al., 2009). We then review studies that report a main effect of sex or sex by age interaction in a sample of adolescents. These findings represent indirect influences of puberty on white matter development in light of evidence suggesting that puberty typically begins earlier in girls (7–13 years old) than boys (9–14 years old) (Grumbach & Styne, 2003). This sets the stage for our critical review of the current literature pertaining to puberty-specific influences on the development of white matter in the adolescent brain. Findings are discussed in terms of their implications for elucidating potential vulnerability markers for affective disorders in at-risk youth.

## 2. Articles selected for review

For this review, we conducted a 2-step literature search. First, we conducted a comprehensive PUBMED search in the English-language literature to identify putative MRI studies that focus on the effects of puberty and/or sexual hormones on brain structure (i.e., white matter) in healthy adolescents, with a particular focus on changes in white matter volume and microstructure. In our search, we also included studies that examined developmental changes in brain structure in adolescents but limited our review to studies that reported significant sex differences. The search terms entered in PUBMED were "puberty AND MRI", "puberty AND magnetic resonance imaging", "puberty AND white matter", "adolescents AND MRI". The search also included these terms with DTI or diffusion tensor imaging in place of MRI and magnetic resonance imaging. To qualify for inclusion in this review, studies must have (1) been an original paper published in a peer-reviewed journal, (2) examined white matter volume using MRI techniques such as voxel-based morphemetric (VBM) or white matter microstructure using diffusion tensor imaging, (3) studied healthy participants between the ages of 8 and 18 years, (4) assessed pubertal maturation using either physical examinations, self-reports and/or included hormonal assessments. We also included MRI studies in adolescents even though they did not include pubertal maturation measures. However, such studies had to meet criteria (1) to (3) as well as include analyses that examined main effects of sex and/or age by sex interactions. A listing of all the articles that meet these criteria is given in Table 1, including first author, journal, year of publication, along with some pertinent details about the sample, study design (neuroimaging technique, pubertal maturation assessment), and a summary of the main findings.

In the current review, we excluded studies that focused solely on age-related changes in white matter during adolescence as these studies have been the focus of previous reviews (e.g., Schmithorst & Yuan, 2010). In addition, we excluded studies that included participants with endocrinological disorders (e.g., sex chromosomal aberrations) that may affect pubertal maturation (e.g., pubertas praecox, pubertas tarda, Klinefelter syndrome) as well as studies that included participants at risk for or diagnosed with a medical or neurological disorder. Although these studies may be informative, they introduce potential confounding factors.

## 3. What is puberty?

### 3.1. Definition

Puberty refers to a specific set of processes implicating changes in physical and reproductive maturation. It is often considered as the beginning of adolescence, a developmental period between childhood and adulthood that encompasses changes at multiple levels. This transitional developmental period not only implicates changes associated with hormonal changes but also changes in physical growth, psychological functioning, and social experiences (Dahl & Spear, 2004; Dorn et al., 2006). Here, we focus on the influence of pubertal maturation on the development of white matter. It is important to keep in mind, however, that maturational changes in white matter occurs along with other developmental changes, which, in turn, could indirectly impact brain development (e.g., changes in social experiences) (Forbes & Dahl, 2010; Spear, 2010).

### 3.2. Neuroendocrine changes

Puberty includes important changes in the functioning of the neuroendocrine system (for a review, see Blakemore et al., 2010; Dorn et al., 2006; Shirtcliff et al., 2009). The earliest phase of puberty or "prepuberty", which begins between 6 and 9 years old in girls and about one year later in boys (Cutler et al., 1990; Parker, 1991), involves the rising of androgens that are secreted by the adrenal glands. These include dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and androstendione (Grumbach & Styne, 2003). The rising of these hormones refers to what is known as the beginning of *adrenarche*.

The maturation of primary sexual characteristics (i.e., ovaries and testes) and the full development of secondary sexual characteristics (i.e., pubic hair, breast, and genital development) is associated with the re-activation of the hypo-thalamic-pituitary gonadal (HPG) axis (Delemarre-van de Waal, 2002; Demir et al., 1996).The initial activation of the HPG axis occurs during the fetal and neonatal developmental period. Reactivation of the HPG axis occurs with the pulsating secretion of the luteinizing hormone (LH) and follicle stimulating hormone (FSH) as well as the increased secretion of gonadal steroids. The rising of these sexual hormones represents a second phase of puberty known as *gonadarche*, which begins at about 9–10 years old in girls and approximately 1 year later in boys (Marshall & Tanner, 1969, 1970). This pubertal period includes the onset of menses, or *menarche*, in girls, and the onset of nocturnal emission, or *spermarche*, in boys. Menarche in girls tends to be an event that occurs rather late in the pubertal process. Spermarche in boys represents the transition from prepubertal to pubertal, and occurs on average at approximately 13–14 years old (Marshall & Tanner, 1969, 1970). The development of secondary sexual characteristics occurs gradually and as such, has been organized into

**Table 1**
Peer-reviewed published articles that focus on associations between puberty and white matter development in adolescence.

| Author, Journal | Age at scan | Sample (female/male) | Pubertal assessment | Hormone measures | Type of study (volumetric/DTI) | Analysis | WM regions measured | Puberty effects? Yes/No | Sex differences? Yes/No | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Peper et al. (2008), Psychoneuroendocrinology | 9 years | Twins: monozygotic (11 females, 13 males); dizygotic (9 female, 12 male, 8 opposite sex twins) | Tanner stages: physical observation using questionnaire (Marshall and Tanner, 1969) | Luteinizing hormone (LH) from saliva samples | Volumetric | VBM | Total cerebral WM | Yes | No | Higher levels of LH associated with overall WM volume and regional WM volume including higher WM density in part of L cingulum, middle tempral gyrus bilaterally, R superior frontal gyrus, splenium of the corpus callosum—both sexes |
| Peper et al. (2009a), Human Brain Mapping | 9 years | Twins: monozygotic (23 females, 22 males); dizygotic (21 female, 22 male, 19 opposite sex twins) | Tanner stages: physical observation using questionnaire (Marshall & Tanner, 1969); created "Tanner status" of 0 or 1 to describe changes in Stages 1 and 2 present in current sample. | None | Volumetric | VBM | Total cerebral WM | Yes | Yes | Exploratory findings: onset of secondary sexual characteristics of puberty associated with increase in occipital WM density. |
| Peper et al. (2009b), Psychoneuroendocrinology | 10–14.9 years | *n* = 78, 41 females, 37 males | Tanner stages: physical observation using questionnaire (Marshall & Tanner, 1969); created "Tanner status" of 0 or 1 to describe changes in Stages 1 and 2 present in current sample. | Testosterone from saliva samples and estradiol from urinary samples | Volumetric | VBM | Total cerebral WM | No | Yes | No associations between hormonal measures and WM—both sexes. *Note*: *girls were older than boys and more advanced in their stages of pubertal maturation.* |
| Perrin et al. (2009), NeuroImage | 12–18 years | *n* = 408; 204 females, 204 males | Self-report using the Puberty Development Scale (PDS) (only stages 3, 4, 5 were included in analyses due to few subjects in stages 1 and 2) | None | Volumetric | Volume and magnetization transfer ratio (MTR) | Total cerebral WM | Yes | Yes | (a) Pubertal maturation associated with greater WM volume in frontal, parietal, and temporal lobes in boys only; (b) pubertal maturation negatively predicted WM MTR in parietal and occipital lobes in boys only; (c) voxel-wise analyses suggested a pubertal stage-related decrease in WM density in putative cortico-spinal tract in boys only. *Note*: *girls more advanced in pubertal maturation than boys in this sample.* |

Table 1 (*Continued*)

| Author, Journal | Age at scan | Sample (female/male) | Pubertal assessment | Hormone measures | Type of study (volumetric/DTI) | Analysis | WM regions measured | Puberty effects? Yes/No | Sex differences? Yes/No | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Perrin et al. (2008), Journal of Neuroscience | 12–18 years | *n* = 408; 204 females, 204 males | Self-report using the Puberty Development Scale (PDS) | Testosterone from blood samples | Volumetric | Volume and magnetization transfer ratio (MTR) | Total cerebral WM | Yes | Yes | (a) Sharper increase in WM volume in boys than girls; (b) association between testosterone and increase in WM volume greater in boys with shorter androgene receptor (AR) gene, suggesting a moderating effect of AR genotype on the relationship between testosterone and WM volume. |
| Asato et al. (2010), Cerebral Cortex | 8–28 years | *n* = 114; 63 females, 51 males | Tanner Maturational Scale self-report questionnaire (drawings); groups: pre/early pubertal group (score 1, 2), midpubertal (score 3, 4), postpubertal (score 5) | None | DTI: FA, RD | Tract-Based Spatial Statistics (TBSS): FA, RD | Whole-brain and ROI | Yes | Yes | [Voxel-wise ROI analyses yielded 19 separate RD clusters that showed significant association with age. For each of these 19 RD clusters, separate group comparisons were performed based on age group, puberty group and sex.] Puberty main effect: only the occipital portion of the left inferior fronto-occipital fasciculus/inferior longitudinal fasciculus (IFOF/ILF) showed maturity during the midpubertal. The other clusters (SLF, UF, CST, IC, CR, ATR, and CC) continued to show immaturity. Sex by age group interaction (l eft IC and right ATR): (a) collapsing across groups, females showed an earlier maturation than males, (b) for females, all clusters showed maturity by adolescence except for the one cluster in right frontal SLF that matured later, (c) for males, all clusters showed ongoing maturation into young adulthood, except for right IFOF/ILF and parietal SLF that showed no differences across age groups. *Note: The methodological design did not allow to parse out effects specific to age vs. puberty.* |
| *Sex differences* | | | | | | | | | | |
| Giedd et al. (1999) | 4–22 years | *n* = 145; 56 females, 89 males; longitudinal study, *n* = 233 scans | N/A | N/A | Volumetric | Combination of analytical techniques including classification of tissues based on voxel intensity and non-linear registration of template brain for which the tissues were manually defined. | Total cerebral WM | N/A | Yes | (a) WM volume increased linearly with age; (b) the WM volume linear increase with age was greater in males than females. |

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|---|---|---|---|---|---|---|---|---|---|---|
| Lenroot et al. (2007), NeuroImage | 13.5–21 years | $n = 367$; 158 females, 209 males; longitudinal study, $n = 829$ scans | N/A | N/A | Volumetric | Automated technique developed at the Montreal Neurological Institute (MNI) | Total cerebral WM | N/A | Yes | (a) total WM volume increased with age in both males and females; (b) after covarying for total brain volume, the shape, but not the height, of the WM trajectory in frontal lobe was different between males and females; the height, but not the shape of the WM trajectory was different between males and females, suggesting that males continued to have larger WM volumes in childhood and adolescence; (c) WM trajectories for temporal lobes, parietal lobes, and caudate were not different between males and females; (d) the mid-sagittal area of the corpus callosum was larger in females than in males. |
| Tiemeier et al. (2010), NeuroImage | 5–24 years | $n = 50$; 25 females, 25 males; longitudinal study, $n = 183$ scans | N/A | N/A | Volumetric | Parcellation of cerebellum | Total and regional cerebellar volumes; longitudinal assessment | N/A | Yes | Overall cerebellar volume larger in males than females, after correction of total brain volume. Sex difference in cerebellar volume decreased with age approaching proportionate differences associated with brain volume in adulthood. Later peak cerebellar volume in males than females. |
| De Bellis et al. (2001), Cerebral Cortex | 6–17 years | $n = 118$; 57 females, 61 males | Tanner staging; method to determine Tanner staging unknown | N/A | Volumetric | VBM | Total cerebral WM | Yes | Yes | Sex by age interaction: Males had a 45.1% increase in total WM volume and 58.5% increase in corpus callosum area. Females had 17.1 and 27.4% increases, respectively. Sex by Tanner stage interaction was also significant for WM volume and corpus callosum area. Main effect of sex: no significant sex differences in WM volumes and corpus callosum areas, after controlling for cerebral volumes (males > females). |
| Giorgio et al. (2008), NeuroImage | 13.5–42 years; adolescents (13.5–21 years); adults (23–42 years) | $n = 62$; 42 adolescents (20 females) and 20 adults (9 females) | N/A | N/A | DTI: FA | Tract-Based Spatial Statistics; voxelwise and tractography | Whole-brain | N/A | No | N/A |

Table 1 (*Continued*)

| Author, Journal | Age at scan | Sample (female/male) | Pubertal assessment | Hormone measures | Type of study (volumetric/DTI) | Analysis | WM regions measured | Puberty effects? Yes/No | Sex differences? Yes/No | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Schmithorst et al. (2008), Human Brain Mapping | 5–18 years | *n* = 106; 54 females, 52 males | N/A | N/A | DTI | SPM5 whole-brain and return ROI: FA and MD | Total cerebral WM | N/A | Yes | *FA*: Sex by age interaction: (a) females had a positive correlation with age and males had a negative correlation with age in right arcuate fasciculus, (b) females had significant positive correlation with age, but not males, in right frontal and right occipito-temporo-parietal WM. Main effect of sex: (a) greater FA in females than males in splenium of the corpus callosum, (b) greater FA in males than females in frontal WM areas bilaterally, right arcuate fasciculus, left parietal and occipito-parietal WM. *MD*: Sex by age interaction: (a) females had a negative correlation with age in frontal lobes bilaterally, in right arcuate fasciculus, and occipito-parietal areas, (b) males had a significant negative correlation in right hemispheres, and no correlation in frontal lobe. Main effect of sex: (a) greater MD in males than females in corticospinal tracts bilaterally and right frontal lobe, (b) greater MD in females than males in right arcuate fasciculus, right occipito-parietal WM, most superior aspect of the corticospinal tract in right hemisphere. |
| Bonekamp et al. (2007), NeuroImage | Mean age = 13.7 ± 3.5 years (age range 5.5–19.1 years) | *n* = 40; 18 females | N/A | None | DTI: ADC, FA | | ROIs: temporal, frontal, anterior limb of the internal capsule, posterior limb of the internal capsule, genu, splenium, body of the corpus callosum, anterior white matter, temporo-occipital, superior longitudinal fasciculus, superior corona radiata, superior fronto occipital fasciculus, cingulum, centrum semi oval e | | | Higher ADC in temporal white matter in males (3.8%) than females and higher ADC in the cingulum in females (1%) than males; no significant sex by age interactions. |

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|---|---|---|---|---|---|---|---|---|---|---|
| Silveri et al. (2006), Magnetic Resonance Imaging | Mean age = 12.3 ± 2.9 | *n* = 21; 12 females, 9 males | N/A | N/A | DTI: FA | In-house Interactive Data Language-based functional MRI[fMRI Analysis Tool]: FA and trace | 3 ROIs: genu and splenium of the corpus callosum, left and right anterior regions of the forward-projecting arms of the WM adjacent to the anterior cingulate cortex | N/A | Yes | FA: Sex by region interaction: (a) greater FA in males than females in left anterior region of the genu of the corpus callosum, (b) greater FA in right anterior region and splenium in females than in males, Trace: Sex by region interaction: not significant. No significant sex by age interaction. |
| Tamnes et al. (2010), Cerebral Cortex | 8–30 years | *n* = 168; 87 females, 81 males | N/A | N/A | Volumetric; DTI: FA, MD, RD, DA | Automated cortical parcellation, regional WM volume; DTI: Freesurfer | Total cerebral WM | N/A | No | Only found sex differences in total WM volume and therefore regressed out effects of sex on all analyses. |

*Notes:* DTI: diffusion tensor imaging, WM: white matter; VBM: voxel-based morphometry; L; left; R: right; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity; ROI: region-of-interest; ADC: apparent diffusion coeffecients; SLF: superior longitudinal fasciculus; UF: uncinate fasciculus; CST: corticospinal tract; IC: internal capsule; CR: corona radiata; ATR: anterior thalamic radiation; CC: corpus callosum.

stages (e.g., Tanner stages), which has allowed clinicians and researchers to assess variations in pubertal maturation.

### 3.3. Measures of puberty in adolescence

Because pubertal maturation involves a complex and gradual developmental process that implicates various endocrine and physical changes, it is important that researchers give careful consideration when selecting a measure of pubertal maturation. The selection of this measure will depend on the nature of the research question (Dorn et al., 2006; Shirtcliff et al., 2009).

There are two types of measures that can be used to assess puberty: physical measures and hormonal measures. One of the most widely used physical measures of puberty is the Tanner stages. Tanner (1962) described five stages of puberty ranging from 1 (no development) to 5 (adult development) (Tanner, 1962). The "Tanner stages" capture visible secondary sexual characteristics such as pubic hair growth and breast/genital development. Typically, the measurement of pubertal status according to this method involves a physical exam conducted by a nurse or physician that employs Tanner's method (Dorn et al., 2006). Although such a method can provide a good assessment of pubertal maturation in terms of changes in secondary sexual characteristics, it requires specialized training and can be difficult to accomplish in non-medical settings. In order to overcome such limitations, some groups have adapted the "Tanner stages" into a self-report method. One method, the Picture-Based Interview about Puberty (PBIP), requires adolescents to examine photographs or line drawings of models that map directly onto each of the Tanner stages and to indicate which of the images most closely resembles their own physical appearance (Morris & Udry, 1980). An alternative method is the Pubertal Development Scale (PDS) (Petersen et al., 1988), which is a self-report questionnaire that includes items asking adolescents to answer questions about their physical development but it does not map directly onto the Tanner stages. Although these self-report measures are often used in developmental research studies, there has been little evidence documenting their reliability and concordance with the physical exam. A recent study suggests, however, that the PDS is highly correlated with a physical exam and hormonal measures and may constitute an adequate measure of pubertal maturation (Shirtcliff et al., 2009).

Measuring changes in hormonal concentrations is another method that has been used to assess puberty. Including measures of hormonal concentrations in studies of adolescent development provide important information that can help address specific questions regarding mechanisms underlying neurodevelopmental changes, which are particularly relevant in neuroimaging studies. Studies that have included measures of hormonal concentrations examined changes in concentration of adrenal adrogens, gonadal steroids, and gonadotropins via blood spot, urine, or saliva (Dorn et al., 2006). There are many factors to consider when considering hormonal concentrations in research protocols. For instance, it is important to consider the phase of the menstrual cycle as the hormonal characteristics will be different in girls who have just begun menstruating compared to those who have been menstruating for several years. Other issues include decisions about assay methods, the influence of age, gender, and race, and what substance will be used (e.g., blood, urine, saliva). Dorn et al. (2006) provide a more detailed discussion about these methodological considerations.

The earliest measurable endocrinological marker of puberty is a nocturnal rise in luteinizing hormone produced by the anterior pituitary gland (Delemarre-van de Wall et al., 1991). It is considered as an early marker of puberty as LH-pulses can be detected before the secondary sexual characteristics become visible (Demir et al., 1996). Together with the gonadotropin follicle stimulating hormone, LH stimulates the secretions of gonadal steroids leading to the production of sex steroid hormones (i.e., testosterone and estrogen). Because the beginning of the rising of adrenal hormones is typically not accompanied by any visible external signs of puberty, including measures of hormonal concentrations as part of research designs is critical to addressing puberty-specific questions. Furthermore, because these hormones begin to increase in childhood (earlier in girls than boys), this suggests that researchers need to consider recruiting younger subjects and to take into account the differences in onset of pubertal maturation in boys and girls when determining the age range of their sample. Including LH measures in neuroimaging protocols, for example, would allow researchers to address specific questions pertaining to associations between the timing of the onset of pubertal maturation and brain development and how these changes may be related to changes in behavior in adolescence.

Changes in the release of growth hormone (GH), which underlies changes in physical growth and body size, also occur during pubertal maturation (Reiter & Rosenfeld, 2003). The increases in GH during puberty contribute to accelerated physical growth (particularly increased height velocity) and show a somewhat different pattern in males and females (Parent et al., 2003). However, it is unclear to what extent the increases in GH secretion may specifically impact brain development.

## 4. Measure of white matter development

### 4.1. Volumetric studies

There are several techniques that are being used to examine white matter volume. A number of studies have used manual tracing methods of white matter structures. Although this approach has several strengths such as characterizing volumes based on more accurate boundaries. Manual tracing of white matter structures in the brain is very time consuming and requires considerable expertise to accurately identify structure boundaries. Thus, some researchers have developed automated and semi-automated segmentation tools (e.g., Niogi et al., 2007). These methods are less time-consuming and generate less inter- and intra-rater variability than manual segmentation. Another more commonly used technique is voxel-based morphometry. VBM is an analytical technique within the neuroimaging software Statistical Parametric Mapping (SPM) that uses a voxel-by-voxel comparison of tissue concentration between different groups of

subjects (Ashburner & Friston, 2000). The tissue concentration can be identified as gray or white matter. High-resolution anatomical magnetic resonance images are acquired and submitted to particular preprocessing procedures, which involve spatially normalizing images for all subjects in the study into the same stereotactic space. The next step entails segmenting the images based on the research question (i.e., gray matter or white matter). Then a modulation step can be applied to compensate for the effect of spatial normalization and to allow computation of absolute volume, for instance. The following step is smoothing of the corresponding images. Finally, voxelwise parametric statistical tests are performed to compare the smoothed images between the different groups. Such analyses yield measures of relative concentration of white or gray matter compared to other tissue types within a specific region. Some of these measures include white matter thickness, volume, and density. Thus, there are several types of analysis can be performed to address questions pertaining to these various measures. For instance, studies using "modulated" data focus on differences in volume (i.e., the absolute amount of white matter in different regions). Additionally, studies that use "unmodulated" data focus on identifying differences in white matter density (i.e., concentration or proportion white matter relative to other tissue types within a region). Some developmental studies have interpreted age-related increases in white matter density in terms of changes in diameter or myelination of the axons forming particular white matter fiber tracts (Barnea-Goraly et al., 2005). It is generally recommended to account for overall brain volume in analyses, particularly when focusing on sex differences, given evidence that males typically have overall greater white matter volume than females (Giedd et al., 1997).

### 4.2. Diffusion tensor imaging

Diffusion tensor imaging techniques are used to examine the integrity of white matter tracks. In contrast to volumetric studies, which focus on the proportion of white matter to other tissues in particular regions, DTI provides more specific information about the microstructural components of white matter, including myelination, and axonal organization. It uses the magnetic resonance signal to visualize water movement within axons, which can help characterize axonal microstructure. Information about the diffusion of water is considered as anisotropic because it is directionally predisposed along the parallel axis of axons (Basser & Jones, 2002). Fractional anisotropy (FA) is a frequently used intravoxel metric that yields values between 0 (isotropic diffusion: diffusion that is equal in all directions) and 1 (maximum anisotropic diffusion: the hypothetical case of diffusion along one axis). Thus, voxels containing water moving predominantly along the principal diffusion direction, rather than the transverse direction, have higher FA. FA is sensitive to a number of neurobiological characteristics of white matter such as axonal size, density, and organization as well as the degree of myelination (Paus, 2005, 2010). Thus, greater FA could reflect greater myelination of white matter fibers, greater number of myelinated fibers, or greater longitudinal versus oblique directional alignment of fibers. Another DTI measure that is often used is radial diffusivity (RD) (Hasan, 2006). RD is an index of diffusivity in directions that are perpendicular to the principal axis of diffusion (i.e., an average of the transverse directions). Mean diffusivity (MD) is also often used as a metric in DTI studies and is an index of the mean overall diffusion. Some studies also report changes in apparent diffusion coefficient (ADC), which is a metric of the magnitude of diffusion within white matter tissue. ADC measures provide information about the properties of diffusion (i.e., rate of water diffusion) occurring within a particular voxel and can then be mapped as an image, using diffusion as the contrast. Moreover, low ADC values are associated with more organized white matter fiber tracts whereas high ADC values are associated with more disorganized tracts. Furthermore, a technique called tractography is used as a way to determine the structure of neural tracts (Correia et al., 2008). Tractography is performed using DTI. It is a method used to examine inter-voxel diffusion coherence capable of producing images of gross white matter organization in the brain. White matter tracts are segmented by starting at a 'seed point' with streamlines fitted through consecutive voxels. Thus, the topography of the tracts resulting from tractography is highly dependent on the seed location. This analytical process requires a minimum number of image acquisition parameters and as such involves a longer scanning session but it can provide a rich description of the structure of white matter tracts.

## 5. Sex differences and white matter in adolescence

Sexual dimorphism (i.e., sex differences in brain structure and function) of the brain in animals and humans has been the focus of numerous research studies over the past century (Allen & Gorski, 1986, 1990; Benes et al., 1994; Giedd et al., 1997). Early work in this area, primarily in rats, focused on the effects of sex steroids hormones on brain morphology during critical developmental periods (for a more detailed review, see McEwen, 1983). Human neuroimaging studies have documented sexual dimorphism in several brain regions including the hypothalamus, the amygdala, the hippocampus, the striatum, the cerebellum, and various regions of the cerebral cortex (e.g., Giedd et al., 1996; Murphy et al., 1996; Paus et al., 1996; Tiemeier et al., 2010). With regard specifically to white matter, most of the findings pertain to tracts involved in interhemispheric connectivity (Allen & Gorski, 1987; Highley et al., 1999; Nopoulos et al., 2000; Witelson, 1989), such as the corpus callosum (Shin et al., 2005). Such differences in interhemispheric connectivity might be related to sex differences in structural and functional hemispheric asymmetry (e.g., Galaburda et al., 1990; Witelson & Nowakowski, 1991; Zaidel et al., 1995). Most of these human neuroimaging studies, however, were conducted in adults. Focusing on adolescence may help elucidate potential developmental mechanism toward sexual dimorphism of white matter.

Several studies report sex differences in the development of white matter during adolescence (Lenroot & Giedd, 2010). As described in the above section, puberty onset occurs generally later in males than females. Thus, findings from studies that report significant sex-related

differences (sexual dimorphism) or sex by age interactions in a sample of subjects in early- or mid-puberty could be interpreted in terms of puberty-specific changes. That is, even though certain MRI studies do not include direct measures of pubertal maturation (e.g., hormone levels, self-report), findings indicating significant sex differences and sex by age interactions could be interpreted in terms of hormonal influences on white matter development or onset of puberty (see Table 1).

With regard to white matter volume, one of the first studies to examine longitudinal changes in white matter volume in childhood and adolescence reported significant sex differences (Giedd et al., 1999). In particular, this large longitudinal study reported significantly less linear increase in white matter volume with age in females than males. A more recent and even larger longitudinal study in normally developing youth ($n = 387$, ages 3–27 years old, scanned every two years) also demonstrated that neurodevelopmental trajectories of white matter were significantly different in males than in females (Lenroot et al., 2007). Total white matter volume increased with age in both males and females, with peak volumes observed at 14.5 years in males and 10.5 years in females. Although gray matter volumes also followed the inverted U shape and peaked earlier in females, white matter continued to increase in both males and females. In particular, white matter volume increased linearly at a faster pace in males than in females, which contributed to the greater white matter in males than females as a function of age. After covarying for total brain volume, there were significant sex-related differences in shape and height of trajectories in individual regions (Lenroot et al., 2007). In particular, there were sex differences in the developmental trajectories of white matter in the frontal and occipital lobes. The shape of the trajectory was different between males and females in the frontal lobe and the height of the trajectory of the occipital lobe was different suggesting that males have larger white matter volumes in childhood and later in adolescence. Furthermore, the mid-sagittal area of the corpus callosum was larger in females than in males.

A more recent longitudinal morphometric MRI study documented sex-differences in the developmental trajectory of the cerebellum (Tiemeier et al., 2010). Although the organization of white matter within the cerebellum is somewhat distinct compared to the rest of the brain, there is evidence suggesting that cerebellar volume may be influenced by pubertal maturation (Ikeda & Nagai, 2006). A total of 50 individuals between the age of 5 and 24 years were scanned at least three times at approximately 2-year intervals. Results indicated that the total cerebellum volume was larger in males than in females and followed an inverted U shape peaking later in males (i.e., 15.6 years) than in females (i.e., 11.8 years), which is consistent with previous longitudinal findings (Lenroot et al., 2007; Sowell et al., 2003). Furthermore, there were significant sex differences in the trajectory of subregions of the cerebellum. For instance, after covarying for total brain volume, the superior and inferior posterior lobes were significantly larger in males than females. These regions play an important role in the inhibition of involuntary movement via inhibitory neurotransmitters, especially GABA, which are relevant for the regulation of behavior and emotion (Quirk & Beer, 2006). There was also evidence of effects related to laterality, with a significant sex by age interaction in the right superior posterior lobe. The cerebellum contains estrogen and progesterone receptors, which suggests that pubertal maturation most likely influences developmental changes in this region (Ikeda & Nagai, 2006). Given the role of the cerebellum not only in motor function but also in higher-order executive function and emotion (Schutter & Van Honk, 2009; Stoodley & Schmahmann, 2010) as well as its implication in neurodevelopmental disorders (e.g., ADHD and schizophrenia), such findings have important implications for the investigation of specific neurodevelopmental markers of vulnerability or risk for psychiatric disease (Baldaçara et al., 2008; Rapoport et al., 2000).

Other studies have used cross-sectional designs to examine sex differences in white matter volume. Using VBM, De Bellis et al. (2001) reported a significant sex by age interaction, suggesting that males had a 45.1% increase in total white matter volume and 58.5% increase in corpus callosum area as a function of age whereas females had a 17% and 27% increases, respectively (De Bellis et al., 2001). This effect was also present when analyses were conducted with Tanner stage measures. These cross-sectional findings are inconsistent with findings from previous cross-sectional studies reporting the absence of sex differences in white matter, which may be associated with methodological and sample size differences (Jernigan & Tallal, 1990; Pfefferbaum et al., 1994). Nevertheless, they suggest differences in age-related changes in white matter between males and females, which are consistent with findings from longitudinal studies (Giedd et al., 1999). Males and females not only differ in relative white matter volume, with males having greater volume than females, they also differ in the ratio of neurons to neuronal processes (i.e., transmission of signal between neurons) (de Courten-Myers, 1999). That is, females tend to have greater neuronal processes and lower neuronal numbers compared with males. One hypothesis is that white matter tracts may include fewer, but thicker and more organized fibers, in males but more crossing fiber tracts in females (Schmithorst et al., 2008). If this is the case, then there may be a differential influence of pubertal maturation on the microstructure and organization of white matter tracts in males and females that could help explain these sex differences in white matter volume and neuron to neuronal process ratio. It is, therefore, possible that sex differences may be better captured using neuroimaging techniques that assess the microstructual organization of white matter. Recent studies have begun to use DTI to examine the influence of puberty on white matter microstructure, providing complimentary findings to volumetric studies.

A recent DTI voxelwise study investigated age-related structural white matter changes in adolescence in a group of 42 healthy adolescent subjects (22 males, 20 females; age range 13.5–21 years, using a novel DTI approach to test for voxelwise correlations between diffusion parameters and age within each age group (Giorgio et al., 2008). Although the authors report significant increase in FA and decrease in perpendicular diffusivity, they did not report any sex differences or sex by age interactions (Giorgio et al.,

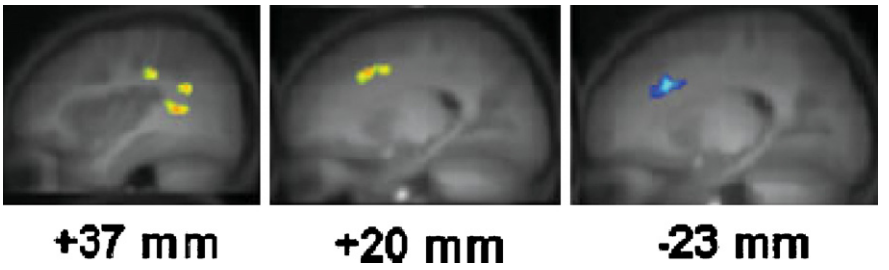


**Fig. 1.** Regions with a significant sex–age interaction on FA (blue = boys > girls, yellow-red = girls > boys) in a cohort of 105 children ages 5–18 years. Slice location (L-R; Talairach coordinate system) given at bottom of each frame. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
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2008). This may be due to the fact that the study included mostly older adolescents in mid- to late-puberty as well as young adults and that the adolescents had an uneven male:female ratio. However, another voxelwise DTI study in a larger sample ($n = 106$) of children and adolescents (ages 5–18 years) did find sex differences in white matter FA in the corpus callosum (Schmithorst et al., 2008). Specifically, there were sex differences in the splenium of the corpus callosum, with FA being greater in females than in males. Findings also indicated greater white matter FA in bilateral frontal regions, right arcuate fasciculus, and in left parietal and occipito-parietal regions (Fig. 1) and greater MD in the corticospinal tract bilaterally and in the right frontal lobe in males than females. Furthermore, there were significant sex by age interactions suggesting that white matter FA in the right arcuate fasciculus, right frontal and right occipito-temporal-parietal tended to increase with age in females. Conversely, in males, FA decreased with age in the right arcuate fasciculus and there were no significant relationships between age and white matter FA in the right frontal and right occipito-temporal-parietal regions. Furthermore, compared to males, females had a faster decline of MD in white matter with age in bilateral frontal regions, the right arcuate fasciulus, and right occipito-parietal white matter. An ROI-based study also found sex differences in apparent diffusion coefficients in white matter (Bonekamp et al., 2007). ADC represents properties of diffusion occurring within a particular voxel. Although the main goal of this study was to investigate intra-rater, inter-rater, and between-scan reproducibility of ADC and FA measurements, they reported sex differences in ADC but not FA. Findings indicated higher ADC in temporal white matter in males (3.8%) than females and higher ADC in the cingulum in females (1%) than males (Bonekamp et al., 2007). None of the analyses in this study, however, showed a significant sex by age interactions in ADC or FA. Another ROI-based study examining the relationship between white matter microstructure and impulsive behavior and response inhibition in a group of adolescents ($n = 21$; age = 12.3 years old) reported significant sex differences in particular white matter tracts (Silveri et al., 2006). ROI analyses focused on the genu of the corpus callosum yielding greater FA in the left anterior region of the genu in males than females and greater FA in the right anterior region and splenium of the genu in females than in males. However, there were no significant sex by age interactions. Interestingly, there were significant sex differences in the relationship between FA and performance on a response inhibition task, with greater FA in right anterior callosum for males and greater FA in the splenium for females being associated with better performance on the task across all subjects (Silveri et al., 2006).

To our knowledge, there has been only one study that used DTI with a longitudinal design to examine white matter development in a large sample ($n = 168$) of children, adolescents, and adults ranging in age from 8 to 30 years old (Tamnes et al., 2010). This recent study reported age-related changes in cortical thickness, white matter volume, and FA. However, sex differences was included as a covariate after preliminary analyses showed significantly larger white matter volume in males than females and because preliminary analyses did not yield significant sex differences or sex by age group interactions. Unfortunately, a covariate interaction term was not included in their model and as a result there was no examination of potential sex by age interactions.

Evidence from these studies suggests that the timing of white matter development is significantly different across the sexes and the fact that white matter volume peaks earlier in girls than in boys suggests that developmental changes in white matter volume might be influenced by puberty. DTI studies provide evidence that in addition to differences in white matter volume, there also appears to be differences in the timing of changes in microstructure.

## 6. Puberty-related influence on white matter development in adolescence

Investigating sex differences is one approach to begin to understand the influence of puberty on white matter development. A more direct approach is to include measures of pubertal maturation such as self-report, physical exams, or saliva or blood essays of reproductive hormones. In addition to such measures, researchers need to consider sex differences in puberty onset when recruiting their research participants. Here, we review findings from research studies that included one of the above approaches to examine associations between puberty and white matter development.

### 6.1. Volumetric studies

Peper and colleagues were one of the first to conduct a number of studies designed to specifically examine the influence of puberty on gray and white matter in adolescents. In a large VBM study ($n = 104$) of monozygotic ($n = 24$) and dizygotic ($n = 29$) 9-year-old twin-pairs, Peper et al. (2008) examined the relationship between levels of luteinizing hormone, which is considered as one of the first endocrinological markers of puberty in both boys and girls, and gray and white matter structure (Peper et al., 2008). They also measured secondary sexual characteristics of puberty using a Tanner-staging questionnaire. Results showed a significant correlation between higher levels of LH and the proportion of overall white matter volume. Higher levels of LH were also correlated with higher regional white matter density in the left cingulum, the middle temporal gyrus bilaterally, superior frontal gyrus, and the splenium of the corpus callosum (Fig. 2). Because the study included twins, the authors were able to document that associations between LH and white matter density may have a common genetic origin (Peper et al., 2008).

In a subsequent study, Peper et al. (2009b) investigated the extent to which global and regional gray and white matter volumes may be heritable across puberty (Peper et al., 2009b). This study included a total of 210 healthy 9-year-old children, including 45 monozygotic and 62 dizygotic twin pairs. In this study, only secondary sexual characteristics were measured using a Tanner-staging questionnaire. Because of the young age of the participants in this study (i.e., 9-year-old children), the authors created a Tanner status measure that captured both adrenal and gonadal maturation. Findings indicated that regional white matter densities of the bilateral fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, the genu of the corpus callosum, and left cingulum were highly heritable. However, there were no significant associations between global white matter volume or regional white matter density and puberty-onset.

In another study, Peper et al. (2009a) examined the influence of sex steroids (i.e., testosterone and estradiol) on global and regional gray and white matter volumes in a sample of 78 children between 10.0 and 14.9 years old (37 boys and 41 girls). Testosterone was collected in saliva and estradiol in urine samples. Samples were collected on two consecutive days and averaged for analytical purposes. Results showed that, unlike findings for gray matter, there was no relationship between testosterone or estradiol levels and global white matter volume or regional white matter density in boys or girls (Peper et al., 2009a).

Other groups have also examined the influence of pubertal maturation on white matter development. For instance, Perrin and colleagues examined the influence of pubertal maturation on white matter volume and magnetization transfer ratio (MTR), which provides information regarding white matter integrity at the macromolecular level and is thought to serve as an indirect proxy of myelination (Perrin et al., 2009). In this study, participants ($n = 408$, 204 males, 12–18 years old) were normally developing adolescents between mid- to late-puberty, which was determined using the Peterson Development Scale. The study involved examining the effects of age, sex, and pubertal maturation and their interaction on measures of white matter density and MTR using a whole-brain approach (Perrin et al., 2009). Findings indicated that white matter density in frontal, parietal, and temporal lobes increased with pubertal maturation in boys only. MTR, however, was negatively related to pubertal maturation in parietal and occipital lobes in boys. Also, white matter density decreased as a function of pubertal maturation in boys in the region of the cortico-spinal tract. In another study including the same sample of adolescents, Perrin et al. (2008) examined the relationship between white matter density, MTR, and pubertal maturation, which was characterized using the Peterson Development Scale (Perrin et al., 2008). They also examined the relationship between blood levels of testosterone and white matter volume and genotyped their participants for a functional polymorphism in the androgen receptor (AR) gene in order to examine the role of the AR receptor in moderating the relationship between testosterone and white matter. Findings from this study revealed a relationship between levels of testosterone and white matter growth in males but not in females. Furthermore, such a relationship in males appeared to be moderated by the presence of androgen receptors as this increase in white matter volume in males was greater in those with the shorter versions of the AR gene (i.e., fewer number of CAG-repeats in this gene).

Findings from these studies demonstrate associations between hormonal changes with puberty and white matter volume. Furthermore, it appears that such associations may be moderated by genetic predispositions.

### 6.2. Diffusion tensor imaging

To our knowledge, only one study has examined the association between pubertal maturation and DTI-measures in a large sample of adolescents. Asato et al. (2010) used both whole-brain and ROI analyses to examine age-, sex-, and puberty-related changes in white matter microstructure in 114 children, adolescents, and adults (Asato et al., 2010). In this study, white matter microstructure was characterized using a radial diffusivity index and pubertal maturation was assessed using the Tanner Maturation Scale, which is a picture-based self-assessment of changes in secondary sexual characteristics. Researchers generated composite scores reflecting breast development and pubic hair development (females) and genital and pubic hair development (males). Subjects were grouped according to the estimated Tanner stage score: pre/early pubertal (scores 1, 2), midpubertal (score 3, 4), and adult maturational/postpubertal (maximum score of 5). Findings from this study indicated that a number of white matter tracts (e.g., uncinate fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, corpus callosum) did not fully mature until the postpubertal stage. The authors interpreted these findings as an indication that pubertal maturation was implicated in the development of these tracts (Asato et al., 2010). It is important to note, however, that age and puberty were tightly coupled in this sample and as such, it is difficult to disentangle the effects of age from the effects of puberty on the development of

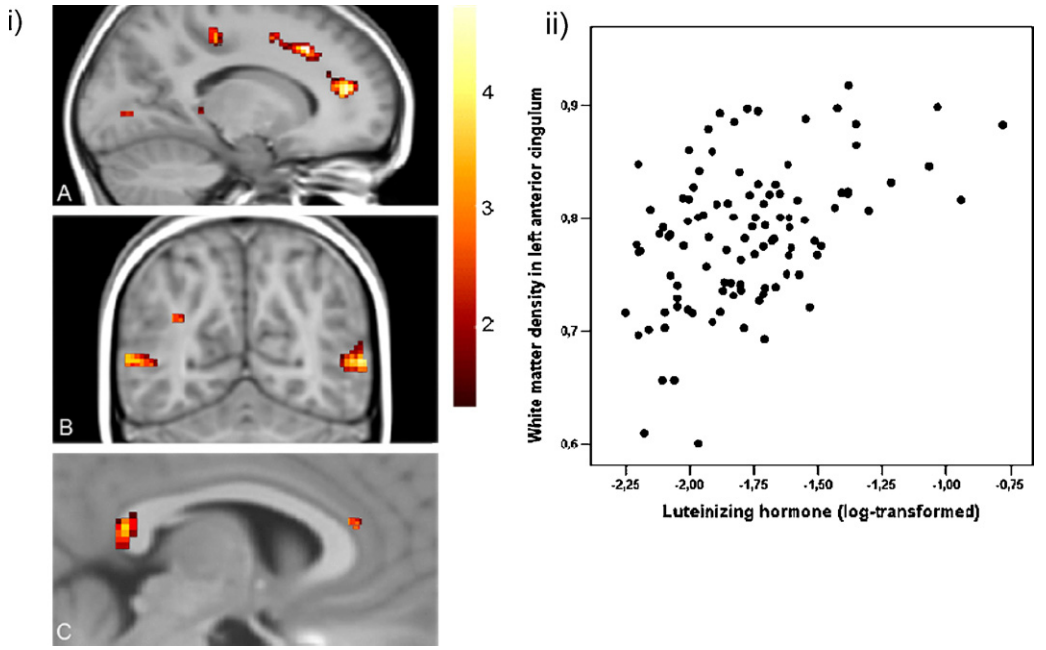


**Fig. 2.** Luteinizing hormone (LH) and changes in white matter density in 9-year-old children. Specifically, the images on the left (i) depicts positive phenotypic associations between LH level and regional white matter density in 104 9-year-old twins. (A) Left cingulum, (B) bilateral middle temporal gyrus, (C) splenium of the corpus callosum. Displayed are *z*-values. The critical *z*-value was 3.39 (corrected for multiple comparisons according to the false discovery rate, $a = .05$). The scatterplot on the right (ii) depicts a phenotypic association between LH level and white matter density in the left anterior cingulum. Depicted are LH levels versus white matter densities in the left anterior cingulum (Talairach *x*, *y* and *z* coordinates −13, 23 and 36). The phenotypic correlation coefficient is 0.44 (95% CI = 0.26–0.58). The LH-values are log-transformed and ranged between −2.25 and −.78, corresponding to LH values ranging between 0.056 and 0.167 U/l (divided by creatinine-level). The actual raw uncorrected LH values range between 0.1 and 1.1 U/l.
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these white matter tracts. When examining findings with regard to main effect of sex or sex by age interaction, results suggest that most white matter tracts reached maturation earlier in girls than boys, except for the right superior longitudinal fasciculus (SLF) that showed ongoing maturation into early adulthood. Such earlier maturation in girls could thus be interpreted in terms of puberty-related changes. Focusing analyses on a subset of subjects within a specific age-range in girls and boys separately and examining associations between pubertal maturation measurements and DTI indices would have helped elucidate further the influence of puberty on white matter development.

## 7. Summary

Studies that have examined associations between puberty and white matter development are limited. Nevertheless, findings from the studies reviewed here suggest that there may be unique pubertal influences on white matter development in adolescence. Volumetric longitudinal studies suggest sex differences in the age at which males and females reach peak white matter volumes, with males reaching white matter peak volumes later than females but at a faster pace. There also appears to be sex differences in corpus callosum white matter development, with greater increase in corpus callosum white matter volume with age in males than females. Sex differences in FA in sub-regions of the corpus callosum were also documented, including sex-related differences in the relationship between FA and impulsive behavior in the right anterior callosum for males and in the splenium for females (Silveri et al., 2006). Together, these findings indicate that sex may impact the timing of white matter development as well as the myelination and organization of specific white matter tracts. Indeed, DTI findings suggest that certain white matter tracts (i.e., splenium) appear to organize faster in females than males. Given that puberty typically begins earlier in females than males (Styne & Grumbach, 2002), we argue that such differences in the timing of white matter development or changes in microstructure may possibly be associated with the onset of puberty. We must acknowledge, however, that other factors could also explain such sex by age interactions associated with white matter development (e.g., genes on sex chromosomes may be turned on or off by certain environmental factors that typically take place in adolescence). Including specific and appropriate measures of pubertal maturation combined with adequate research designs would help minimize such confounding effects.

Findings from studies that included direct assessment of pubertal maturation provide some exciting clues about the specific relations between puberty and white matter development. In particular, research from Peper and colleagues suggest that pubertal hormones may impact white matter development in prepubertal adolescents, before the appearance of any physical changes with puberty. For instance, they documented that early-secreted hormones such as LH influence white matter density of specific

inter-hemispheric and association tracts in both males and females. Others demonstrated that influences of pubertal hormones on white matter development may be moderated by genetic predisposition. For instance, Perrin and colleagues reported that the influence of testosterone on white matter volume was greater in boys with shorter versions of the androgen receptor gene. Only one study, to our knowledge, reported associations between pubertal maturation and microstructure of specific white matter tracts in adolescence, suggesting that puberty may influence the maturational process of certain white matter tracts differently in boys and girls.

Despite the limited number of studies and variations in methodological procedures and dependent variables, findings suggest that pubertal hormones may influence the timing and organization of regional white matter development differently in boys and girls and that such influence may be moderated by genetic predisposition. It is important to note, however, that changes in white matter volume or FA associated with pubertal maturation could be related to a number of factors. For instance, such changes could be related to progressive age-related axonal myelination (Benes, 1994; Yakovlev & Lecours, 1967), or alternatively, to increasing axonal calibre (Paus, 2010). Such controversies pertaining to the biological processes implicated in white matter maturation have been discussed by Paus and colleagues and require further study (Paus, 2005, 2010). Another important issue to consider is the causal relationship between pubertal maturation and changes in white matter. Evidence from animal studies suggest that glial cells, which are responsible for the production of myelin, have the capacity to regulate the secretion of sex steroids (i.e., glial steroidogenesis) (Garcia-Segura & Melcangi, 2006). Such potential reciprocal dynamic relationships between the secretion of pubertal hormones and white matter development attests to the complexity of elucidating the specific developmental mechanisms underlying the specific influence of puberty on white matter development (Peper et al., 2011). Furthermore, although some studies used a longitudinal design, most of the studies used a cross-sectional design. Cross-sectional designs provide initial data regarding developmental changes but they present some limitations with regard to inferring developmental processes (Kraemer et al., 2000). Thus, future studies including multiple measures of white matter microstructure (e.g., FA, RD, longitudinal diffusivity, MTR, tractography) as well as longitudinal designs are strongly recommended in order to better understand the nature of the effect of pubertal hormones on white matter development. Until such studies are undertaken, it will be challenging to determine to what extent hormonal changes during puberty and adolescence are causally involved in these white matter maturational processes. Finally, another issue to consider is the methods used to assess pubertal maturation. The above studies used the following strategies: (a) sampling subjects within a limited age-range (e.g., 9-year olds), (b) including similar ratio of male and female participants; and (c) including hormonal measures, self-report questionnaires, or physical examinations to document pubertal maturation. Although most of these studies used these strategies in one form or another, some failed to control for the fact that girls typically mature sexually 1–2 years earlier than boys and included boys and girls within the same age range (12–18 years old, 8–28 years old) (e.g., Perrin et al., 2009; Asato et al., 2010). Moreover, some did control for age by recruiting subjects within a narrow age range (e.g., Peper et al., 2009b) but there were age differences between boys and girls yielding the possibility that the males in the samples of the above studies were in earlier stages of pubertal development compared to their female counterparts. An attempt was made to address this issue by examining associations between sex and brain structure within each sex separately (Peper et al., 2009b). These issues are particularly relevant also in light of recent animal work indicating that males and female brains respond differently to changes in steroid hormones, suggesting that complex interactions between sex and pubertal hormones also need to be taken into consideration (Galea, 2008). Despite some of these methodological issues, the above findings can provide promising clues about the specific influence of pubertal maturation on white matter development. Such clues are important to elucidate neurodevelopmental trajectories associated with increased risk for psychopathology.

## 8. Puberty-related changes in white matter development and implications for affective disorders

There is mounting evidence suggesting that adolescence is a sensitive period for the onset of behavioral and emotional health problems (Dahl & Spear, 2004; Steinberg et al., 2006). In particular, adolescence represents the period with the greatest increase in risk for the development of affective disorders, especially in girls (Angold et al., 1995, 1998; Angold & Worthman, 1993). Recently, there has been an emerging literature documenting alterations in white matter microstructure in individuals diagnosed with affective disorders, including major depression and bipolar disorder (Kafantaris et al., 2009; Sexton et al., 2009; Versace et al., 2008; Zhu et al., 2011). Such alterations in white matter have also been reported in youth at high familial risk for these affective disorders (Hajek et al., 2005; Huang et al., 2011; Versace et al., 2010).

Structural as well as functional neuroimaging studies suggest that corticolimbic systems are implicated in the pathogenesis of affective disorders, especially ventromedial-amygdala and frontal-thalamic-striatal systems (Mayberg, 2001; Phillips et al., 2008; Price & Drevets, 2010; Savitz & Drevets, 2009). Neuroimaging studies indicate that these neural systems are also involved in the processing and regulation of emotions (Phillips et al., 2008), which undergo important developmental changes in adolescence (Ernst et al., 2006; Monk et al., 2003; Steinberg, 2005). Therefore, puberty-specific influences on white matter development in adolescence may influence connections between neural regions implicated in emotion processing and regulation thereby potentially impacting the functioning of these neural systems. Given evidence that puberty onset is occurring at a younger age in industrialized countries (Euling et al., 2008), it is possible that puberty-related changes in white matter microstructure

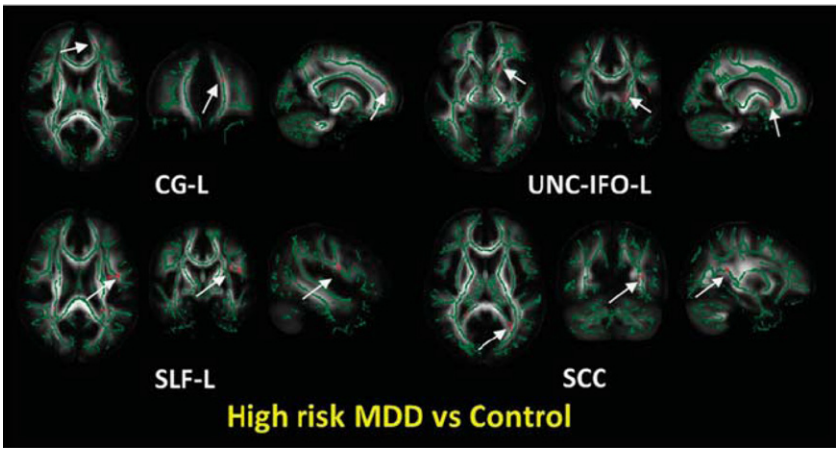


**Fig. 3.** FA reductions in healthy adolescents at high familial risk for unipolar depression compared to healthy controls. Specifically, the significant clusters obtained from voxel-wise comparisons between control and high-risk groups. Green color indicates white matter skeletons, and red color shows clusters with significant FA reduction in the high-risk group ($p < 0.001$). Underlying gray scale images are the averaged FA maps, depicting different tracts. The left, middle, and right columns of each panel show the images of axial, coronal, and sagittal views, respectively. White arrows indicate clusters of the specified white matter tracts in the left cerebral hemisphere if multiple clusters are shown in the image. FA, fractional anisotropy; CG-L, left cingulate, SLF-L, left superior longitudinal fasciculus; SCC, splenium of the corpus callosum; UNC-IFO-L, left uncinate-inferior fronto-occipital fasciculus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
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may influence both the structure and function of neural systems of emotion processing and regulation and that such developmental changes may render particularly vulnerable youth (i.e., genetic predisposition, early-life stressors) at increased risk for affective disorders. For example, a recent DTI study showed lower FA in the cingulum bundle, the splenium of the corpus callosum, and the uncinate fasciculus in healthy adolescents at high familial risk for unipolar depression compared to healthy controls (Huang et al., 2011). Evidence reviewed here suggests that the splenium of the corpus callosum, organizes faster in girls than in boys (Silveri et al., 2006). Based on these, although somewhat limited, findings it would be plausible to hypothesize that puberty-related changes in the splenium of the corpus callosum, for example, may represent a potential vulnerability marker for future onset of affective disorders in high-risk youth. The uncinate fasciculus is another white matter tract that appears to be relevant to the risk for affective disorders. It is a large fiber track connecting three key regions involved in emotion regulation (i.e., amygdala, lateral and medial prefrontal cortex) (Highley et al., 2002). Asato et al. (2010), reviewed here, indicate that it is one of the white matter tracts that reaches maturation earlier in girls than boys. Moreover, several studies have documented abnormalities in the microstructure of the uncinate fasciculus in individuals diagnosed with an affective disorder (Cullen et al., 2010; Versace et al., 2008; Wang et al., 2009) and more recently, in youth at high familial risk for affective disorders (Huang et al., 2011) (Fig. 3).

Whether puberty-mediated alterations in the development of these and other white matter tracts may contribute to the development of affective disorders in adolescence remains to be investigated. Such hypotheses would need to be tested using longitudinal studies with larger samples of at-risk youth combined with genetic information (Raznahan et al., 2010) and accurate measurement of pubertal maturation to determine whether puberty-related changes in these white matter tracts indeed represent neurodevelopmental markers of risk for affective disorders. Nevertheless, these examples illustrate the need for a more in-depth understanding of the developmental mechanisms underlying changes in white matter development (Paus et al., 2008)—an endeavor that may require multi-level approaches and inter-disciplinary collaborations.

## 9. Conclusions and future directions

In this review, we presented a critical review of research findings indicating associations between pubertal maturation and white matter development. We showed that some studies reporting sex differences in white matter development with age may reflect possible changes associated with pubertal maturation. Very few studies have investigated puberty-specific influences on white matter development in adolescence. These emerging findings suggest that pubertal hormones influence specific regions of white matter and that such influences may be associated with certain genetic predispositions. These findings are relevant in light of recent findings reporting altered development of white matter implicated in emotion processing and regulation in individuals diagnosed with affective disorders as well as youth at high familial risk for these disorders. Much more research is needed to elucidate further the developmental mechanisms underlying white matter changes in adolescence and how such changes influence the functioning of complex neural systems that govern regulation of emotion and behavior.

Advances in neuroimaging techniques offer valuable tools that have yet to be adopted by researchers focusing on adolescent brain development. For instance, recent

advances in the field of diffusion imaging offer the possibility of being able to perform high-definition fiber tracking (HDFT) (Fernandez-Miranda et al., 2010; Verstynen et al., 2011). HDFT provides higher resolution of white matter fascicles and the visualization of complex crossing fibers, which is currently impossible with standard DTI techniques (Alexander and Barker, 2005). Such high resolution techniques have the potential to better track developmental changes in white matter in adolescence and address issues regarding timing of changes in white matter microstructure. However, the current HDFT data acquisition protocols last approximately 40 min, which would be challenging for many children and adolescents to complete. Perhaps future developments in HDFT methodology will enhance the feasibility of this technique with young people. Other research avenues include the development of image acquisition techniques that serve to document specific changes in myelin (Deoni et al., 2011, 2008). Although DTI measures offer some metric about white matter microstructure, changes in these measures may not be specific to myelin content alteration (Beaulieu, 2002; Paus, 2010). Deoni et al. (2008) developed a novel MRI technique called multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT), which they describe as a new time-efficient multicomponent relaxation (MCR) analysis. This novel technique, which has recently been used in infants (Deoni et al., 2011), provides a more sensitive and specific examination of white matter maturation. This technique therefore has the potential to document myelin changes in the adolescent brain and how such changes may be influenced specifically by pubertal maturation.

The paucity of research studies documenting specific puberty-related influences on white matter development attests to the fact that this is an area of research that is still emerging. Incorporating methodological procedures from the field of developmental psychology and neuroendocrinology along with innovative neuroimaging techniques and data analytical procedures from the fields of physics and neuroscience represents a promising research avenue in advancing our knowledge about adolescent brain development and the identification of potential neurodevelopmental markers of risk in vulnerable youth.

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