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Girls' pubertal development is associated with white matter microstructure in late adolescence

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ABSTRACT

Patterns of pubertal maturation have been linked to vulnerability for emotion dysregulation disorders in girls, as well as white matter (WM) development, suggestive of a potential mechanism between pubertal maturation and emotional health. Because pubertal processes begin at varying ages (i.e., status, timing) and proceed at varying rates (i.e., tempo), identifying individual differences in the pubertal course associated with subsequent WM microstructure development may reveal clues about neurobiological mechanisms of girls' emotional well-being. In a prospective cohort study of 107 girls, we examined associations between pubertal status at age 9, pubertal timing and tempo from ages 9–15, and WM microstructure at age 19. Tract-based spatial statistics revealed that girls with more advanced pubertal status at age 9, specific to gonadal-related physical changes, had higher fractional anisotropy, and lower mean diffusivity (MD) and radial diffusivity in tracts relevant to cognitive control and emotion regulation (e.g., the superior longitudinal fasciculus, external capsule, and uncinate fasciculus). Additionally, girls with earlier pubertal timing showed lower MD in the left anterior cingulum bundle. Tempo was unrelated to WM measures. These findings implicate specific aspects of pubertal maturation in subsequent neural signatures, suggesting possible neuroendocrine mechanisms relevant to emotional development. Future work incorporating longitudinal neuroimaging in parallel with pubertal measures may contribute to the understanding of individual variation in pubertal course and WM development.

1. Introduction

Puberty-driven changes of the adrenal and gonadal axes have lasting impacts on brain maturation, including strengthening of neural connections that organize and foster the acquisition of cognitive abilities and social behaviors required for meeting the developmental challenges of adolescence and early adulthood (Sisk and Zehr, 2005). Pubertal changes contribute to the maturation of nerve fibers in the brain's white matter (WM) tracts (Perrin et al., 2008), which connect regions critical for cognitive processing (Liston et al., 2006). Long-range connectivity of networks supporting emotion regulation and response to stress is modified by the rise of pubertal hormones (Bale and Epperson, 2015), potentially leading to enduring differences in WM microstructure. In girls, pubertal status (i.e., physical characteristics in relation to peers), timing (i.e., the age at which a given pubertal event has occurred), and tempo (i.e., the speed at which pubertal processes occur) have been associated with subsequent development of disorders involving emotion dysregulation (Angold et al., 1999; Keenan et al., 2014; Mendle et al., 2007).

Although some work in mixed-sex studies has yielded concurrent links between pubertal status and WM (Asato et al., 2010; Herting et al., 2017, 2012; Menzies et al., 2015), associations between dimensions of girls' pubertal development over time and subsequent variation in WM tracts following the completion of puberty have not yet been explored. Such an approach may reveal potential mechanisms or mediators of pubertal maturation and later emotional health to target for clinical

Abbreviations: WM, white matter; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity.

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intervention. As a first step towards this goal, the current study sought to test the direct relationships among several dimensions of pubertal development (i.e., pubertal status in childhood, and pubertal timing and tempo modeled across ages 9–15 years) and brain WM microstructural characteristics (age 19) after completion of the pubertal process in a sample of girls.

Perceptions of greater relative growth, as well as early timing and faster rate of physical changes are linked to a number of negative social-contextual experiences (e.g., low socioeconomic status, harsh parenting) and psychological difficulties (e.g., depression, risk-taking) for girls (see review by Mendle et al., 2007). Data from the Pittsburgh Girls Study, a community-based sample of 2450 girls, revealed that pubertal status, timing, and tempo were associated with the emergence of depression (Keenan et al., 2014). Approximately 30% of the girls reached Tanner stages 3 or 4 by age 9 and those with earlier pubertal timing (age at Tanner stage 2) showed higher depressive symptoms early on (age 10) whereas girls with faster tempo (more accelerated rate of pubertal maturation from ages 9–17 years) showed increasing depressive symptoms from ages 10–13 years (Keenan et al., 2014). The findings from Keenan and colleagues support the off-time/maturational deviance hypothesis (Simmons and Blyth, 1987) and suggest that a different timing or rate of pubertal development from peers may confer risk for depression. Deviations from on-time/average pubertal trajectories also may relate to brain development, where one's relative pubertal status at an early age, earlier timing, or faster progression may alter the normative influence of pubertal hormones on the changing organization of WM tracts over time.

Human and rodent studies document that adolescence is accompanied by profound WM proliferation, followed by selective synaptic pruning of unused connections (Bourgeois and Rakic, 1993; Giedd et al., 1999). Greater WM availability and subsequent pruning contributes to enhanced neural signaling and transmission among some WM tracts at the expense of other unused connections. In humans, myelination of most WM tracts during adolescence occurs at a rapid rate, a process that in part is postulated to account for cognitive, emotional and social maturation (Barnea-Goraly et al., 2005), and continues into adulthood (Lenroot and Giedd, 2006).

Pubertal development includes adrenarche (i.e., maturation of the adrenal system), and gonadarche (i.e., maturation of the hypothalamic-pituitary-gonadal axis), as well as growth of secondary sex characteristics, all of which are changes driven by increases in estradiol in girls, testosterone in boys, and adrenal hormones in both sexes (Berenbaum et al., 2015). Both adrenal hormones (e.g., DHEA; Dehydroepiandrosterone) and gonadal sex steroid hormones (e.g., oestradiol, testosterone, progesterone, and estrogen) are involved in brain development. DHEA is an adrenal steroid that has been implicated in relation to neuroprotection and neurite growth (Maninger et al., 2009) as well as modulation of cortical thickness (Nguyen et al., 2017, 2013). In addition to adrenal hormones, animal studies point to the clear role of gonadal hormones for stimulating neuronal growth and synaptic branching, as well as facilitating myelination, the process by which oligodendrocyte cells insulate WM axon bundles with fatty phospholipid sheaths. Progesterone, for example, facilitates oligodendrocyte activity (Baulieu and Schumacher, 2000), and estradiol and progesterone stimulate the proliferation of Schwann cells, which produce myelin proteins (Fex Svenningsen and Kanje, 1999). These findings are corroborated in human studies pointing to a relation between testosterone levels and structural development of WM tracts (Pangelinan et al., 2016). Additionally, evidence suggests that gonadal hormones increase axonal caliber in males (Herting et al., 2012; Menzies et al., 2015) and myelination in females (Perrin et al., 2009).

Importantly, the timing of puberty influences the levels of secreted sex steroids that alter neuronal growth and glial cell activity in WM (Cooke and Woolley, 2005). What distinguishes earlier and later maturers is that gonadarche-induced hormones are not only secreted at an earlier age, but also at higher levels, which may persist into adulthood. For example, a longitudinal study of 200 girls revealed that a younger age at menarche was accompanied by larger increases in serum estradiol compared to older onset (Apter and Vihko, 1985). Because pubertal timing affects the level of secreted hormones, which directly influence the growth of WM, it is plausible that individual differences in facets of pubertal maturation forecast variation in WM, yet this remains to be tested. In line with neurobiological perspectives of early puberty (Dahl, 2004), we tested the hypothesis that when the body secretes pubertal, specifically gonadal, hormones at an earlier age and at higher levels, the brain may experience accelerated proliferation and subsequent fine-tuning of WM development in adolescence.

Several key WM tracts have more pronounced developmental maturation throughout adolescence, including projection tracts, which carry signals from the cerebrum to the rest of the body; commissural tracts, which integrate signals across hemispheres; and association tracts, which connect various cortical and subcortical regions. Microstructural properties of WM tracts are commonly characterized using Diffusion Tensor Imaging (DTI), a method that measures the directional diffusion of water, which informs the organization of WM fibers. As axons thicken from the myelination of directionally oriented fibers, diffusion becomes highly anisotropic, or restricted to a principal directional axis (Alexander et al., 2007). The most commonly examined measure derived from DTI data is fractional anisotropy (FA), which indexes the fraction of magnitude of a diffusion tensor, or anisotropic diffusion (Basser and Pierpaoli, 1996). While FA is sensitive to most WM pathological conditions, multiple scalar measures of the diffusion tensor have also been examined (Alexander et al., 2007), including mean diffusivity (MD), which relates to the inverse of membrane density (Feldman et al., 2010), and radial diffusivity (RD), which quantifies non-restricted water flow and correlates highly with WM dysmyelination (Alexander et al., 2007; Song et al., 2002). Although DTI does not measure WM myelination directly, the microstructural properties of water diffusion are discernable noninvasive markers of cell density and proliferation status (Beppu et al., 2005).

Consistent with the postulation that WM tracts become more highly organized in a directional matter to facilitate transmission and coordination of signals, patterns of increasing FA and decreasing MD and RD during adolescence and early adulthood within most tracts have been reported (Giorgio et al., 2010; Mukherjee et al., 2001; Schmithorst et al., 2002). For example, in a study of 78 children, adolescents, and young adults, age-related increases in FA in the superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), and anterior thalamic radiation (ATR) were observed, with results more pronounced in the left than in the right hemisphere (Peters et al., 2012). Additionally, in a study of WM maturation in 202 individuals ages 5–30 years, age-related increases in FA and decreases in MD were observed across 10 tracts, including the corticospinal tract (CST), cingulum, SLF, IFOF, and uncinate fasciculus (UF) (Lebel et al., 2008). Along with increases in FA and decreases in MD, a study of 8–30 year olds found decreasing RD across a wide range of WM tracts (Tamnes et al., 2010). Prolonged maturation in adolescence and adulthood supports the development of motor skills (via the CST) (Kolb and Whishaw, 2015), emotion processing (via the cingulum and UF) (Coad et al., 2017; Keedwell et al., 2016), and cognitive control (via the SLF, corona radiata, and posterior thalamic radiation) (Chaddock-Heyman et al., 2013). The normative patterns of WM development, typically increasing FA and decreasing MD and RD, in these fundamental tracts have been explored in relation to age, sex, and concurrent pubertal status.

WM microstructure also differs between males and females, suggesting that sex-specific differences in pubertal hormones may play an important role in brain WM development (Ladouceur et al., 2012). For instance, females peak in WM volume and reach tract diffusion maturation (via FA and RD) at earlier ages than males. Beyond the general role of sex differences, individual variation in pubertal development could be an additional factor in the variability of WM development. Indeed, RD decreases as pubertal status increases in the UF, SLF, ATR, and corpus callosum (CC) (Asato et al., 2010). Physical changes associated with puberty also predict increases in FA in the thalamus, superior corona

radiata (CR), CC, and superior frontal gyrus in sex-specific ways (Herting et al., 2017). Sex differences in the timing of puberty and WM neuroanatomy suggest the utility of studying the sexes separately, in order to elucidate more distinctly the effects of pubertal processes on WM. One study of 12–16 year-old boys reported that more advanced pubertal status predicted lower MD in the SLF and inferior longitudinal fasciculi (ILF), UF, CST, ATR, cingulum, and forceps minor and major (Menzies et al., 2015). A more fine-grained assessment of puberty across development, within a single-sex, same-age cohort, would more fully capture how variability in pubertal processes, beyond chronological age, may affect WM microstructure. However, no previous research has tested how individual differences in pubertal trajectories may relate to WM microstructure in late adolescence, when cognitive and affective systems are undergoing significant rewiring and behavioral consequences ensue (Jalbrzikowski et al., 2017; Somerville et al., 2010).

1.1. Current study

The current study examined girls' WM microstructure at age 19 as a function of their pubertal status at age 9, and pubertal timing and tempo across ages 9–15 (modeled using growth curve analysis). In addition to testing contributions of overall pubertal status, we separated self-reported physical maturation into indicators of adrenal and gonadal development to estimate whether an axis superseded the other in its association with WM microstructure. We expected that (1) girls who were more advanced in pubertal status at age 9 would show higher FA, and lower MD and RD in late adolescence (age 19), reflecting a hastened WM development trajectory; (2) gonadal, rather than adrenal indicators of physical growth, would underlie the association between age 9 status and subsequent WM measures (based on the effects of progesterone and estradiol on axonal development) (Baulieu and Schumacher, 2000; Fex Svenningsen and Kanje, 1999); and (3) girls with earlier pubertal timing and (4) faster tempo would show higher FA, and lower MD and RD at age 19. We expected puberty-related differences in FA, MD, and RD to emerge in association and projection tracts that show protracted maturation and support cognitive control and emotion regulation development, including the UF, SLF, CR, and CC (Asato et al., 2010).

2. Material and methods

2.1. Participants

Participants were 107 girls recruited from the longitudinal Pittsburgh Girls Study (Keenan et al., 2008). In the PGS, a stratified, random household sampling method, with over-sampling of households in low-income neighborhoods, was used to identify girls between the ages of 5 and 8 years. Of the 2992 eligible families, 2450 (85%) agreed to participate in the prospective study. At age 9, the youngest of the participants were recruited for a sub-study on emotion (Keenan et al., 2010), aimed at assessing precursors of depression. Eligibility for the PGS-E was determined based on either screening high on depressive measures at age 8, or by selection of the remaining youngest participants. Of the 263 families deemed eligible, 232 agreed to participate and completed the first laboratory assessment at age 9. Girls participated in annual MRI scanning beginning at approximately 16 years of age. At the third MRI time-point (when most girls were 18–19 years old), a diffusion MRI scan was introduced to the neuroimaging battery. Of the 232 girls enrolled in the PGS-E, 31 refused to participate in the third MRI scan visit, 20 could not be reached, 30 were ineligible (e.g., nonremovable metal in the body, pregnancy, claustrophobia), and 4 completed only behavioral tasks and self-report measures. Although 147 girls were scheduled to scan, neuroimaging datasets were not obtained for 21 participants due to time constraints, subject discomfort, or scanner and data transfer issues. Of the remaining 126, 11 participants were excluded from analyses due to excessive movement or poor coverage of whole brain regions, leading to 115 available neuroimaging datasets. Further, participants scoring under 70 points on the Verbal IQ (Wechsler, 1991) scale were excluded from analyses in order to reduce the potential for misreporting or lack of understanding on the pubertal measure ($n = 8$) and to control for effects on WM microstructure (Dunst et al., 2014).

Sixty-four percent of the final 107 participants were African American ($n = 68$), 31% were European American ($n = 33$), and 5% were multiracial or of another race ($n = 6$). To address the small sample size of the multiracial/other group, two groups were created for analyses, where 0 = European American and 1 = African American or Multiracial. Given documented associations between race and factors of pubertal development (Keenan et al., 2014), racial status was treated as a covariate in examining associations between pubertal dimensions and DTI measures. Written assent/consent was obtained for all participants and their parents. Participants were compensated monetarily for their participation. All study procedures were approved by the Institutional Review Board of the university where the study was conducted.

2.2. Procedures and measures

2.2.1. Pubertal development

Pubertal status was assessed with the self-reported Petersen Physical Development Scale (PPDS) (Petersen et al., 1988) annually from ages 9–15 years. Previous studies show strong correlations between self-reported and physician ratings of pubertal status even in children under age 9 (Carskadon and Acebo, 1993). The PPDS includes four questions about growth spurt, pubic and axillary hair, breast development, and changes in skin rated on a four-point scale (1 = has not yet begun; 2 = has barely started; 3 = is definitely underway; 4 = seems completed) and one yes/no question about menstruation onset. Summary scores of girls' pubertal maturation each year were calculated by averaging the five questions, where the menstruation item was recoded to 1 (has not started) and 4 (started). Though Keenan et al. (2014) used measures of breast, hair growth, and menarche to classify girls by Crockett staging in the larger PGS study, the current method allowed us to capture multiple events of puberty associated with both gonadal and adrenal hormonal development on a continuous scale (1 = minimum pubertal maturation; 4 = maximum pubertal maturation), and has been used in previous studies (Beltz et al., 2014; Herting et al., 2017).

2.2.2. Pubertal status at age 9

All girls were born within the same calendar year, which constrained chronological age but allowed variability in degree of pubertal maturation. Pubertal status was operationalized as score at age 9. Items pertaining to height, breast development, and menarche were averaged to create gonadal-based maturation scores. Items assessing hair growth and skin changes were averaged to create adrenal-based maturation scores. This parcellation method has been used in previous studies and correlates strongly with boys' and girls' physical and hormonal exam scores (Herting et al., 2017; Shirtcliff et al., 2009).

2.2.3. Pubertal timing and tempo

Changes in overall pubertal status scores (including menarche, development of breast and pubic hair, and changes in skin and height) across 7 occasions (ages 9–15) were modeled with a non-linear Gompertz growth model (Campbell et al., 2012) (Fig. 1). The model was specified as:

$$f_{it} = (g_1 + (g_1 - g_0)) \times \exp(-\exp(-g_{2i} \times (age_{it} - g_{3i}))) + d_{it}$$

where f_{it}, the observed pubertal status score at assessment occasion t for individual i, is modeled as a function of g_1, the universal upper asymptote (e.g., pubertal status score of 4 or full pubertal maturity); g_0, a universal lower asymptote (e.g., pubertal status score of 1); g_{2i}, an individual-specific pubertal tempo parameter capturing the speed at which an individual progresses from the lower to upper asymptote; g_{3i}, an individually-varying pubertal timing parameter; and d_{it}, the time-

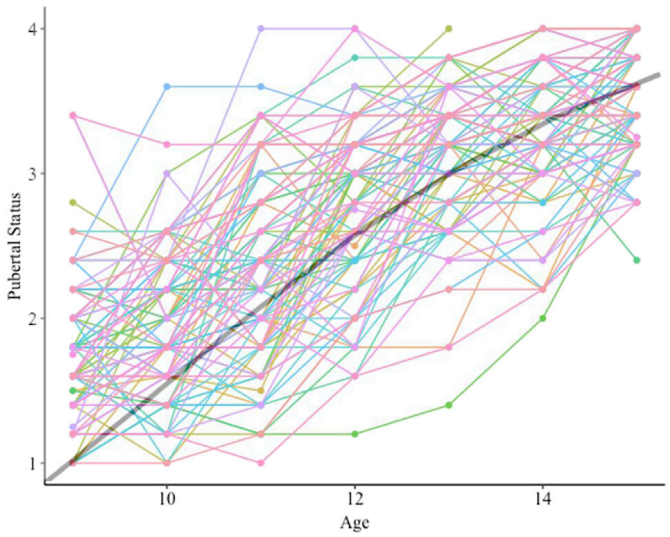

Fig. 1. Ages 9–15 pubertal status with the Gompertz model equation line superimposed.
A nonlinear Gompertz growth model was fit to the seven observed occasions of self-reported pubertal status (including onset of menstruation and changes in body hair, breast, height, and skin) to estimate pubertal timing and tempo from ages 9 to 15. Participants included are from the neuroimaging sample (n = 107).

dependent disturbance score. The upper and lower asymptotes (g_1 and g_0) were fixed to 4 and 1, representing all individuals' progression from pre- to post-pubertal maturation. The model was fit to longitudinal data using SAS PROC NLMIXED to obtain individual-level scores for timing, g_{3i}, and tempo, g_{2i} (Littell et al., 2006). The Gompertz model is asymmetric and approximately 37% of change occurs before the inflection point (Laursen et al., 2013). Thus, timing scores represent when participants are approximately 37% through the process of pubertal development (an approximate pubertal status score of 2.11). While many girls were already past a pubertal status score of 2.11 at the first assessment of age 9 ($n = 22$, 20.56%), the model projects backward to predict approximate timing.

2.2.4. Diffusion MRI scan

Participants underwent a diffusion MRI acquisition during which they laid still on the scanner bed with padding around their heads to reduce movement, and wore earplugs to mitigate noise. During the scan, trained technologists inspected all images for neurological abnormalities. All MRI data were acquired using a 3.0T Siemens Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). Diffusion weighted images were collected using a pulsed-gradient spin-echo sequence applied in 68 directions, with posterior-to-anterior phase encoding. DTI scan parameters included repetition time = 8500 ms, echo time = 91 ms, and field of view = 256 mm^2. Sixty-four contiguous slices were acquired with an isotropic voxel size of 2.0 mm^3 and a *b*-value of 1000 s/mm^2.

2.2.5. Image processing

Data were pre-processed using tools from Functional MRI of the Brain (FMRIB) Diffusion Toolbox, part of FSL 5.0.9 (FMRIB Software Library) (Smith et al., 2004; Woolrich et al., 2009). Images and diffusion gradient vectors were affine registered to the first reference volume ($b = 0$) to correct for eddy currents, head motion, and magnetic field inhomogeneity. Summary motion metrics of displacement, rotation, and translation (Jenkinson et al., 2002) were calculated and included in a motion outlier detection check. Participants with a high relative displacement between each volume acquisition (>3 SDs from mean of 1.10 mm) were excluded ($n = 11$). Brain extraction (skull-stripping) was performed on the remaining participants using FSL's Brain Extraction Tool (Smith, 2002). Images were then visually inspected to ensure proper coverage. Poorly outlined brain data were rerun through skull-stripping with modified parameters. Whole-brain maps of the three orthogonal eigenvectors and eigenvalues were generated by applying a diffusion tensor model in a voxel-wise approach to the data. Using the diffusion information, we then calculated summary measures of fractional anisotropy (FA; a measure of restricted directionality in diffusion of water), mean diffusivity (MD; the average of all three eigenvalues in all directions), and radial diffusivity (RD; the average of two eigenvalues, not including the principal vector).

2.2.6. Tract-Based Spatial Statistics voxel-wise analysis

The Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) toolbox from FSL was used to conduct a voxel-wise statistical analysis of the DTI data. This toolbox provides a pipeline for preparing diffusion data for voxel-wise analysis by first aligning all FA data to a common space, using nonlinear registration in FNIRT (Andersson et al., 2010), and then creating a mean FA image. The mean FA image was thinned to create a mean FA skeleton representing the centers of tracts common to the current sample. Then, all participants' aligned FA data were projected onto the skeleton to create a group-specific skeletonized FA image. This transformation was also applied to the MD and RD data to create skeletonized MD and RD images. Skeleton voxels with a mean FA of <0.2 were excluded to reduce partial volume effects. Voxel-wise between-subjects statistical analyses were then performed on the skeletonized FA, MD, and RD data.

2.3. Data analysis plan

We tested our *a priori* hypotheses that dimensions of pubertal development would predict WM microstructure characteristics in the FA, MD, and RD maps using FSL's "Randomise" tool for voxel-wise analysis (Winkler et al., 2014). All analyses included the covariates of race (0 = European American, 1 = African American/Multiracial or other) (Nyquist et al., 2014), verbal IQ (Wechsler Intelligence Scale for Children-III-R; administered by trained interviewers when the girls were 10 years old) (Dunst et al., 2014; Wechsler, 1991), exact age at scan, and the three summary head motion metrics (Yendiki et al., 2014). Significance was tested within each analysis using 5000 non-parametric permutation tests (Nichols and Holmes, 2002; Winkler et al., 2014) and the threshold-free cluster enhancement (TFCE) correction for multiple comparisons (Smith and Nichols, 2009). Our threshold for significance after TFCE correction at the whole-brain level was $\alpha = 0.05$. Anatomical locations of significant regions on skeletonized maps were identified using the Johns Hopkins University White-Matter Labels and White-Matter Tractography atlases, available through FSL. Four separate regression analyses were conducted in TBSS to test: (a) the main effect of age 9 pubertal status; (b) the main effect of gonadal status at age 9; (c) the main effect of adrenal status at age 9; and (d) the main and interaction effects of pubertal timing and tempo. The magnitude of effect of each variable of interest was computed using Cohen's f^2, which is appropriate for multiple regression models of continuous independent and dependent variables (Cohen, 1988).

Mean FA, MD, and RD values were extracted for the largest significant clusters identified in the TBSS analyses. These values were then used to plot the direction and magnitude of main effects on diffusion measures in R Statistical Software version 3.4.0 (R Core Team, 2017).

3. Results

Table 1 presents descriptive statistics and correlations for verbal IQ, race, pubertal status at age 9 (overall, gonadal, and adrenal), pubertal timing, and tempo across ages 9–15 for participants in the neuroimaging sub-study ($n = 107$).

Although most of the sample reported having started the beginning stages of puberty at age 9 (average score of 1.77 overall, 1.88 gonadal, and 1.64 adrenal), there was still considerable variability in age 9 status

Table 1
Sample means, standard deviations, and correlations.

Variable	*M* (*SD*)	Range	1	2	3	4	5	6	7
1. Age at scan, years	19.28 (0.44)	18.21–20.37	–						
2. Race	AA/MR (N) = 82		$t = 2.30$*	–					
3. Verbal IQ	100.6 (15.44)	70–141	.13	$t = 5.62$**	–				
4. Head movement (mean volume-to-volume displacement, mm)	1.09 (0.18)	0.74–1.67	-.14	$t = -1.31$	.01	–			
5. SES (years with public assistance)	4.83 (4.46)	0–13	0.21*	$t = 5.65$**	-.53**	-.01	–		
Pubertal Dimensions									
6. Pubertal Timing	10.18 (.98)	7.76–12.75	-.18	$t = 2.75$**	.03	.07	.06	–	
7. Pubertal Tempo	0.34 (.058)	0.18–0.47	.23*	$t = -1.19$	.09	.10	-.08	-.45**	–
8. Age 9 Status	1.78 (0.48)	1.00–3.40	-.02	$t = -1.99$*	-.04	-.16	-.07	-.71**	-.11
Age 9 Gonadal Status	1.88 (0.50)	1.00–4.00	-.09	$t = -2.43$*	.04	-.10	-.04	-.63**	-.01
Age 9 Adrenal Status	1.64 (0.63)	1.00–4.00	.08	$t = 0.89$	-.11	.07	-.09	-.55**	-.19*
9. Age 10 Status ($n = 105$)	1.96 (0.50)	1.00–3.60	.17	$t = -2.35$*	-.03	-.10	-.04	-.78**	.14
10. Age 11 Status ($n = 106$)	2.34 (0.63)	1.00–4.00	.16	$t = -2.07$*	.00	-.03	-.01	-.85**	.40**
11. Age 12 Status ($n = 103$)	2.77 (0.57)	1.20–4.00	.16	$t = -2.80$**	-.06	.05	-.07	-.79**	.63**
12. Age 13 Status ($n = 106$)	3.10 (0.48)	1.40–4.00	.25*	$t = -1.71$	-.01	-.04	-.02	-.70**	.74**
13. Age 14 Status ($n = 104$)	3.26 (0.44)	2.00–4.00	.22*	$t = -1.81$	.09	-.05	-.13	-.63**	.74**
14. Age 15 Status ($n = 104$)	3.47 (0.35)	2.40–4.00	.09	$t = -0.23$	.20*	.07	-.16	-.46**	.66**

Note: * indicates $p < .05$; ** indicates $p < .01$. *M* and *SD* are used to represent mean and standard deviation, respectively. *Min* = Minority. All correlations are Pearson correlations. *T* values are indicated where testing for race differences. Results are pertaining to the imaging sample ($n = 107$).

(ranging from scores of 1–3.4, 1–4, and 1–4 in overall, gonadal, and adrenal respectively), with some girls exhibiting signs of earlier development relative to peers (12 had an age 9 overall pubertal status 1 SD above the mean, between 2.24 and 3.4, indicating that one or more features of pubertal growth were underway). An independent-samples *t*-test revealed a significant difference in age 9 overall pubertal status between European American ($M = 1.65$, $SD = 0.43$) and African American/Multiracial ($M = 1.84$, $SD = 0.48$) participants, $t\ (68) = -1.99$, $p = .050$. Age 9 gonadal status was also higher in African American/Multiracial girls ($M = 1.95$, $SD = 0.52$) compared to European American ($M = 1.72$, $SD = 0.43$) girls, $t\ (73.77) = -2.42$, $p = .018$. There was no significant difference in age 9 adrenal status between the 2 groups, $t\ (66.55) = -0.89$, $p = .37$. In line with findings from the larger PGS sample (Keenan et al., 2014), an independent samples *t*-test revealed that African American/Multiracial girls exhibited earlier pubertal timing ($M = 10.00$, $SD = 0.86$) than European American girls ($M = 10.60$, $SD = 1.10$), $t\ (49.89) = 2.75$, $p = .0082$. Contrary to the larger study, however, there was not a significant difference in pubertal tempo between African American/Multiracial ($M = 0.34$, $SD = 0.057$) and European American ($M = 0.33$, $SD = 0.061$) participants, $t\ (58.08) = -1.19$, $p = .24$ (Table 1). The discrepancy between studies on racial differences in tempo may be a function of sample size ($N = 107$ vs. $N = 2450$), selection of participants (those in the current study were recruited based on higher depression symptomatology at age 8), or characterization of pubertal maturation (average score based on PPDS questions vs. grouping based on Crockett staging).

3.1. Age 9 overall pubertal status

3.1.1. FA

More advanced overall pubertal status at age 9 was associated with higher FA at age 19 in seven left-lateralized significant clusters ($p < .05$ corrected). The greatest effects were found in the left anterior, superior, and posterior CR, left CST, left internal capsule (IC), and left UF (maximum voxel $t = 5.21$, $p < .023$). The next strongest effects emerged in the left external capsule (EC), left ATR, and left CST in association with age 9 pubertal status (maximum voxel $t = 3.75$, $p < .044$), along with small portions of the left IFOF, left SLF, and left ILF (maximum voxel $t = 3.51$, $p < .046$; Table 2).

3.1.2. MD

More advanced overall pubertal status at age 9 predicted lower MD in one large cluster ($p < .05$ corrected) including the CC, forceps minor (FM), and bilateral portions of the anterior, superior, and posterior CR, EC, posterior thalamic radiation (PTR), ATR, IFOF, SLF and ILF (Table 2).

3.1.3. RD

Lastly, more advanced age 9 pubertal status was associated with lower RD in four clusters ($p < .05$ corrected), with the largest associations in the FM, and left ATR, anterior and superior CR, left ILF, left IFOF, CC, and left CST (maximum voxel $t = 4.87$, $p < .014$). Three other clusters were associated with age 9 pubertal status and included the right posterior CR, and left IC, EC, and SLF (maximum voxel $t = 4.03$, $p < .05$; Table 2).

3.2. Gonadal vs. adrenal hormonal indicators

Gonadal, but not adrenal, indicators of age 9 pubertal status accounted for the association between early differences in perceived physical growth and WM diffusion measures at age 19 (Table 2). Elevated gonadal-based pubertal status was associated with higher FA in similar regions as found when testing the main effect of overall age 9 status, however clusters expanded to include the genu and body of the CC and right portions of the EC, IFOF, and SLF as well ($p < .05$ corrected; Table 2, Figs. 2a and 3). Similarly, more advanced gonadal-based age 9 status was associated with lower MD in mostly the same WM regions identified in TBSS analysis of overall age 9 status (maximum voxel $t = 4.93$, $p < .05$ corrected; Table 2, Figs. 2b and 3). Parallel to the main effect on FA, greater gonadal-based pubertal status at age 9 was associated with lower RD in many of the same tracts identified in relation to overall age 9 status, with the extension to bilateral regions of the anterior, superior, and posterior CR, EC, SLF, ATR, ILF, IFOF, and SLF (maximum voxel $t = 4.89$, $p < .05$ corrected; Table 2, Figs. 2c and 3). Similar, moderate effect sizes were observed across WM metrics ($0.23 < f^2 < 0.25$).

3.3. Pubertal timing and tempo

Gompertz model-derived pubertal timing, tempo, and the interaction of timing and tempo were simultaneously tested in relation to WM diffusion measures. No significant effects were found in relation to FA or RD. However, earlier pubertal timing was associated with lower MD in one left-lateralized cluster (maximum voxel $t = 4.39$, $p = .046$ corrected, 169 voxels), which included the anterior CR, FM, and anterior cingulum bundle (Table 2, Fig. 4a and b). The Cohen's f^2 effect size of this finding was moderate ($f^2 = 0.18$). There was no significant main effect of tempo, or interaction of timing and tempo, in relation to MD.

Models were rerun without IQ and motion covariates as a validation that inclusion of these factors did not conflate the results. The results of these analyses were consistent with the main findings, with some additional WM areas showing significant associations with pubertal indicators (see supplemental materials: Table 1, Fig. 2a–b, and Fig. 3a–b).

Table 2
Results from Tract-Based Spatial Statistics analyses of age 9 overall pubertal status, age 9 gonadal status, age 9 adrenal status, and pubertal timing and tempo effects on FA, MD, and RD.

Model	Main Effects	Measure	*t*	*p*	Effect Size		Cluster(s)	Region(s)
					r	f^2		
1	Age 9 Overall Status	FA	2.26–5.21	.05–.023	0.21–0.45	0.046–0.25	7	Ant & post IC (l), ACR (l), PCR (l), SCR (l), EC (l), ATR (l), CST (l), IFOF (l), ILF (l), SLF (l), UF (l)
		MD	4.99	.004	0.44	0.23	1	Genu, body, & splenium of CC, ACR (b), PCR (b), SCR (b), EC (b), ATR (b), PTR (b), FM, IFOF (b), ILF (b), SLF (b)
		RD	3.49–4.87	.05–.014	0.32–0.43	0.11–0.23	4	Genu & body of CC, ant & post IC (l), ACR (l), PCR (l), SCR (l), EC (l), ATR (l), CST (l), IFOF (l), ILF (l), SLF (l), UF (l)
2	Age 9 Gonadal Status	FA	2.84–4.76	.05–.03	0.27–0.42	0.078–0.21	3	ATR (b), SCR (b), ACR (b) genu & body of CC, EC (b), CST (l), FM, IFOF (b), SLF (b), IC (b)
		MD	4.93	.01	0.43	0.23	1	Genu, body, & splenium of CC, ACR (b), PTR (b), EC (b), SLF (b), FM, IFOF (b), ILF (b), SLF (b)
		RD	4.89	.01	0.43	0.23	1	Genu, body, & splenium of CC, ACR (b), SCR (b), PCR (b), EC (b), SLF (b), ATR (b), FM, ILF (b), IFOF (b), SLF (b), IC (B)
3	Age 9 Adrenal Status	FA	–	–	–	–	–	–
		MD	–	–	–	–	–	–
		RD	–	–	–	–	–	–
4	Pubertal Timing	FA	–	–	–	–	–	–
		MD	4.39	.046	0.39	0.18	1	ATR (l), FM, ant. cingulum (l)
		RD	–	–	–	–	–	–
	Pubertal Tempo	FA	–	–	–	–	–	–
		MD	–	–	–	–	–	–
		RD	–	–	–	–	–	–
	Timing x Tempo	FA	–	–	–	–	–	–
		MD	–	–	–	–	–	–
		RD	–	–	–	–	–	–

Notes: (l) = left; (r) = right; (b) = bilateral; *r* = correlation coefficient; f^2 = Cohen's f^2 method of effect size. Model 1 tested only the main effect of age 9 pubertal status. Models 2 & 3 tested the main effects of age 9 gonadal and adrenal status respectively. Model 4 tested the main effects of pubertal timing, tempo, and their interaction. Nonsignificant results are omitted. All analyses covaried for age, race, motion, and verbal IQ. FA = Fractional Anisotropy. MD = Mean Diffusivity. RD = Radial Diffusivity. CST = corticospinal tract; SLF = superior longitudinal fasciculus; IFOF = inferior fronto-occipital fasciculus; ATR = anterior thalamic radiation; PTR = posterior thalamic radiation; ILF = inferior longitudinal fasciculus; CC = corpus callosum; ACR = anterior corona radiata; PCR = posterior corona radiata; SCR = superior corona radiata; FM = forceps minor; IC = internal capsule; EC = external capsule; UF = uncinate fasiculus; IC = internal capsule. $N = 107$.

4. Discussion

The current study tested whether individual variation in dimensions of pubertal development, as assessed from late childhood to mid-adolescence, was associated with WM microstructural properties at age 19. We hypothesized that more advanced pubertal status at age 9 would be associated with higher FA, and lower MD and RD in late adolescence, and that gonadal-based physical indicators would underlie these associations. Indeed, more advanced overall pubertal status at age 9 was associated with higher FA in left-lateralized anterior WM regions, including the anterior and posterior limbs of the IC, the anterior, superior, and posterior CR, as well as the EC, ATR, UF, and CST and smaller portions of the IFOF, ILF, and SLF. More advanced age 9 status was also associated with lower MD in the CC and FM and lower RD in the CC and left-confined regions of tracts found in the FA analysis. Parsing of puberty-related measures added to the findings that physical markers of more advanced gonadal, rather than adrenal, development at age 9 were associated with higher FA, and lower RD in the bilateral SLF, ILF, and IFOF, as well as the CC, FM, and left anterior CR. Results suggest discernable neuroendocrine pathways contributing to subsequent WM microstructural differences. Lastly, earlier timing of puberty was associated with lower MD in the left anterior CR, FM, and anterior cingulum. Earlier pubertal timing may be related to an accelerated trajectory of WM maturation, through hastened decline of MD in WM. Although we did not find an association between pubertal tempo and WM metrics, we were only able to characterize the brain's microstructural properties at age 19. Additionally, our findings were specific to girls and underscore the importance of examining sexes separately when measuring relations between pubertal maturation and brain development.

In the US, most girls' breast development is underway by 9 years of age, with pubic hair development occurring before age 9 in African American girls, and by age 10 in European American girls (Herman--Giddens et al., 1997; Susman et al., 2010). Our prospective study was not designed primarily to measure puberty, in which case the epidemiology of pubertal maturation suggests that assessment would ideally begin before age 9. Still, age 9 onset is relatively early in typical pubertal development and girls vary in the timing of normal pubertal events from ages 8 to 15 (Lee and Styne, 2013). Our research extends studies showing associations among inter-individual differences in pubertal status and concurrent WM microstructure by examining how pubertal status at age 9 may relate to WM measures in late adolescence. We hypothesized that more advanced pubertal status at age 9 would be associated with increases in FA, and decreases in MD, and RD within regions found to show protracted maturation in adolescence, including the UF, SLF, ATR, CST, and CC. Indeed, we found higher FA and lower MD and RD in these tracts, as well as the IC, CR, and to some extent the IFOF and ILF. We also hypothesized that earlier pubertal timing and tempo would associate with higher FA and lower MD and RD in similar tracts, though we only found a relationship between timing and MD in the cingulum bundle, CR, and FM. Our findings are consistent with the overall normative pattern of WM development, in which alignment of fibers increases along the main direction of the tract and diffusivity in other directions decreases (Tamnes et al., 2010), particularly within WM regions known to develop into adolescence (Asato et al., 2010) and in parallel with pubertal staging (Genc et al., 2018, 2017; Herting et al., 2017).

All WM regions identified in the current study share critical roles in cognitive and motor functioning in late adolescence, as well as in the orientation and comprehension of socio-emotional information. Inter-hemispheric WM bundles, such as the CC and FM, are critical in integrating motor, sensory, and cognitive information across homologous areas in the adolescent brain (Luders et al., 2010). In addition to tracts involved in improvements in associative function, pubertal status was related to microstructural organization in tracts predominantly involved in motor and sensory function, including the CST (Kolb and Whishaw, 2015). Importantly, the relation between early differences in pubertal status and age 19 WM organization was most pronounced in WM tracts

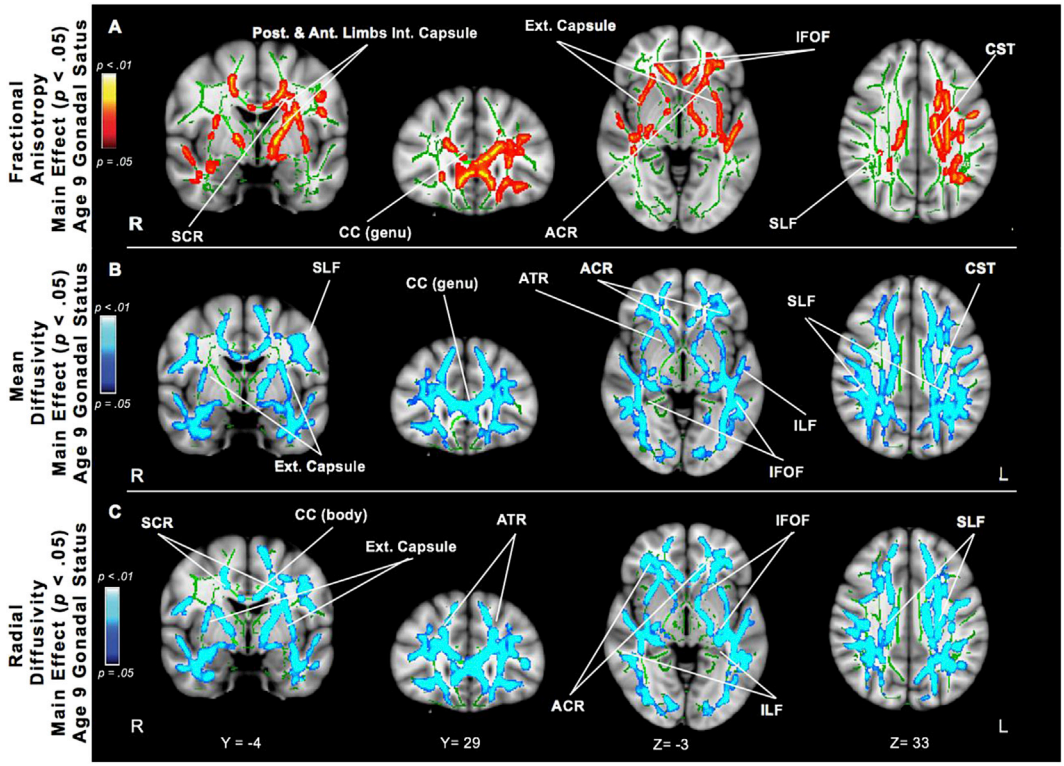

Fig. 2. Tract-Based Spatial Statistics results of main effect of age 9 gonadal status on **(A)** FA, **(B)** MD, and **(C)** RD. Red indicates positive association between pubertal measure and FA. Blue indicates negative association between pubertal measure and MD or RD. All analyses covaried for age, race, motion, and verbal IQ. Ant. = anterior; Post = posterior; CST = corticospinal tract; SLF = superior longitudinal fasciculus; IFOF = inferior fronto-occipital fasciculus; ATR = anterior thalamic radiation; ILF = inferior longitudinal fasciculus; CC = corpus callosum; ACR = anterior corona radiata; SCR = superior corona radiata; Int. Capsule = internal capsule; Ext. Capsule = external capsule; UF = uncinate fasiculus. Regions were identified using the Johns Hopkins University White-Matter Labels and White-Matter Tractography atlases available through FSL. $N = 107$.

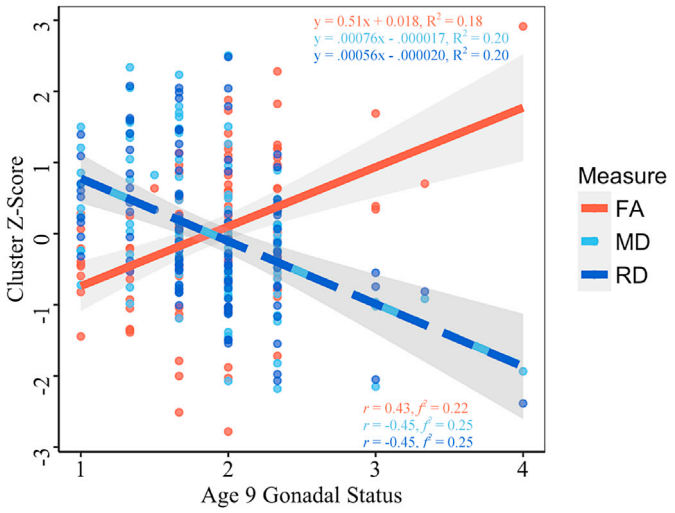

Fig. 3. Main effect of age 9 gonadal status on FA, MD, and RD of largest significant clusters. r = correlation coefficient; f^2 = Cohen's f^2 method of effect size. Tract-based spatial statistics analyses revealed a significant main effect of age 9 gonadal pubertal status on fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) in white-matter tracts (WM) at age 19. More advanced physical maturation in childhood may reflect more mature patterns of WM diffusivity in late adolescence. $N = 107$.

supporting cognitive and emotion processing. For instance, the UF is considered part of the limbic system and carries fibers between temporal regions, such as the hippocampus, and frontal regions, including the orbitofrontal cortex (Schmahmann et al., 2008). The UF has been associated with regulating emotional responses and with performance on emotionally valenced cognitive tasks (Coad et al., 2017; Ghashghaei and Barbas, 2002). Also recognized as a WM tract involved in emotional aspects of attention, memory, and motivation, the cingulum bundle links the rostral and caudal subdivisions of the cingulate gyrus, the dorsolateral-, orbital-, and medial-prefrontal cortices, and temporal areas, such as the parahippocampal gyrus (Schmahmann and Pandya, 2009). We likewise found associations between pubertal status and the SLF, which in part connects motor and prefrontal areas and has previously been implicated in cognitive control performance (Chaddock-Heyman et al., 2013). Furthermore, our results included the EC, which conveys projection fibers from cognitive and limbic regions to the striatum, suggesting a crucial pathway supporting motor, cognitive, and emotion control (Schmahmann et al., 2008). Our findings imply a form of coupling across the pubertal course and subsequent brain development, particularly in WM fiber bundles found to support cognitive control and emotion regulation development. Our results indicate that more advanced physical maturation early on may predict a pattern of faster WM maturation in late adolescence, which was reflected in the current study as higher FA and lower MD and RD at age 19.

The maturational deviance perspective posits that both early and late pubertal development may be associated with social stress and higher risk for psychopathology (Petersen and Taylor, 1980). Our findings showed that girls with earlier pubertal timing showed lower MD in the anterior cingulum bundle, while girls with late pubertal timing exhibited higher MD in the cingulum bundle (Fig. 4). The cingulum has been implicated in a variety of conditions, including depression in adolescents (Cullen et al., 2010). Thus, while MD typically decreases with adolescent development, it could perhaps decrease at a faster rate or reach a lower level in those with earlier pubertal maturation, conferring risk for cognitive and emotional dysfunction. Similarly, late pubertal

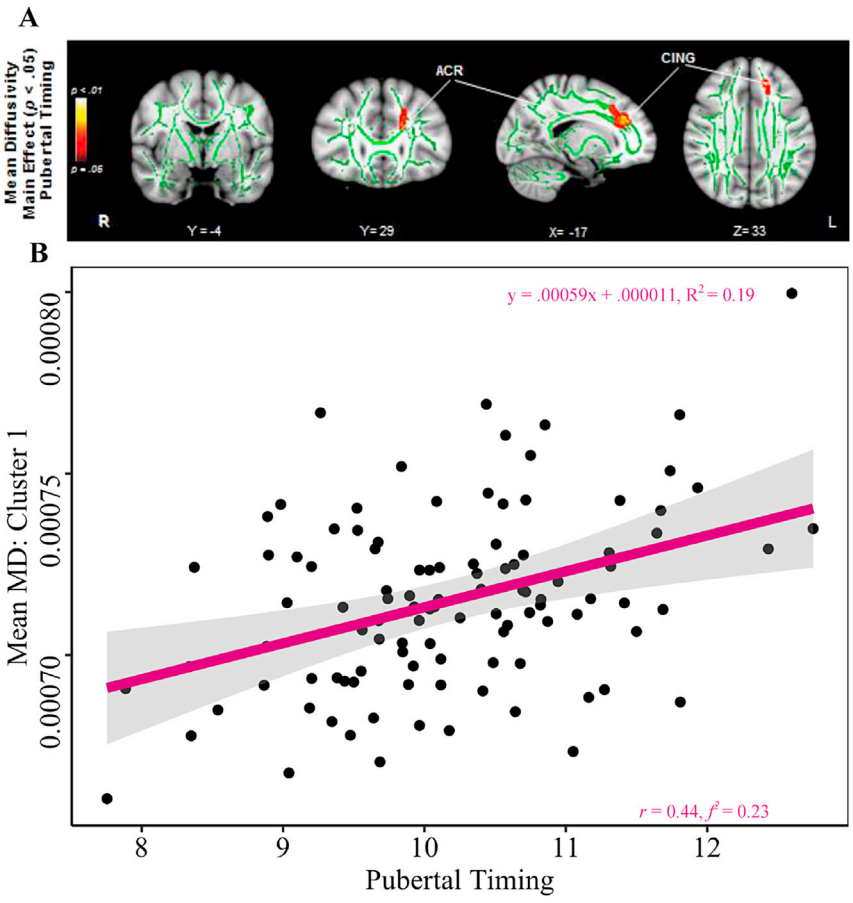

Fig. 4. Tract-Based Spatial Statistics result of main effect of pubertal timing on MD. **(A)**, Earlier pubertal timing was associated with lower mean diffusivity (MD) in a cluster comprised of the left anterior thalamic radiation, left cingulum bundle, and forceps minor at age 19 ($t = 4.39$, $p = .046$). **(B)**, Mean MD values were extracted from significant cluster identified in Tract-Based Spatial Statistics (TBSS) analyses and a regression line was fitted to depict the relationship between pubertal timing and MD; r = correlation coefficient; f^2 = Cohen's f^2 method of effect size. $N = 107$.

development may result in underdeveloped WM microstructure, reflected by low FA and high MD and RD, relative to on-time peers. The protracted maturation of these tracts suggests continued refinement and contributing roles to cognitive control and top-down regulation, a process that may be truncated or incomplete in the face of early or late pubertal maturation. Though our study did not measure WM microstructure longitudinally, it is possible that varying pubertal trajectories affect the speed or pattern of WM changes over time. However, our finding regarding MD and pubertal timing should be taken with caution as the associated WM region was relatively small (169 voxels), and the p value was just below 0.05 ($p = .046$). According to Cohen's guidelines (Cohen, 1988), the effect size of this result was moderate ($f^2 = 0.18$) and warrants further research into the possible relation between pubertal timing and later WM microstructure.

Our analyses revealed that early indicators of gonadal, rather than adrenal, pubertal maturation significantly predicted FA, MD, and RD, offering clues about which endocrine systems may be particularly influential in girls' WM microstructural development. The current findings are in accordance with our hypothesis driven by evidence of gonadal hormonal effects on the process of WM development (Baulieu and Schumacher, 2000; Fex Svenningsen and Kanje, 1999), as well as concurrent associations between gonadal hormones and WM microstructure (Herting et al., 2012; Menzies et al., 2015). Endocrine fluctuations arising from the activation of the HPG-axis may produce lasting differences in WM organization. Previous research examining the effects of gonadal steroids on developing neurobiology supports these claims. The organizational influence of gonadal steroids on the brain has been identified in two critical stages of the lifespan: the perinatal period (McCarthy, 2010) and adolescence (Piekarski et al., 2017; Sisk, 2017; Sisk and Zehr, 2005). Gonadal hormones have been shown to induce synaptic plasticity through their modulatory effects on cells containing sex steroid receptors, including neuronal presynaptic and postsynaptic terminals (Akama and McEwen, 2003), and glial cells (Garcia-Segura and Melcangi, 2006). Estrogen and androgens bind to receptors to stimulate dendritic spine development in certain subsets of cells, while reducing spine density in other subsets (Cooke and Woolley, 2005). Similarly, evidence of testosterone and estrogen effects on axonal sprouting has been found in rodents (Morse et al., 1986). The timing of gonadarche and the magnitude of pubertal hormones secreted may affect how experience-dependent circuits are wired in the critical window of WM refinement during adolescence.

Adrenal hormonal effects on glial cells and neurons have also been documented (Gould et al., 1992), however we were not able to show that early variation in adrenal-based indicators was related to WM measures at age 19 in the current study. Beginning data collection of pubertal indices at age 9 may have been too late to capture early onset of adrenarche (Utriainen et al., 2015), or that adrenal hormones have less detectable effects on the diffusion characteristics we measured at age 19. Future research is needed to replicate these results based on direct measures of both gonadal and adrenal hormone levels to clarify relations between various puberty-induced changes and brain WM development.

We expected that off-time maturation, in the form of earlier pubertal timing, or faster pubertal tempo, would predict similar outcomes at the WM microstructural level. However, we found no associations with tempo or an interaction of timing and tempo on WM. Our neuroimaging data was collected only at one time-point when participants were 19 years of age and the lack of finding for pubertal tempo may be attributed to this limitation. Additionally, while age 9 status was one of the seven observed measures included in our longitudinal Gompertz growth model, it was distinct from our indices of pubertal timing and tempo. Pubertal timing estimated the time at which an individual achieved about 37% of pubertal development, or the point at which the rate of growth was

highest. As expected, more advanced age 9 pubertal status was correlated with earlier pubertal timing. However, the pubertal timing measure accounted for the entire trajectory of intra-individual change, whereas age 9 status was simply a snapshot of inter-individual variability. These distinctions drove the initial analysis plan to examine both age 9 status and pubertal timing, and may underlie the divergent findings. Namely, we found that earlier pubertal timing predicted lower MD in the left anterior cingulum bundle, an area not found in association with age 9 pubertal status. Cingulum MD may relate to variations in the estimated chronological age of the inflection point of the Gompertz growth curve (pubertal timing), whereas the CST and ATR may show sensitivity to early differences in physical maturation at one chronological age.

4.1. Limitations

Limitations must be considered when interpreting the current findings. First, FA, MD, and RD do not measure the same WM structural properties and are not direct measures of myelination or membrane density. While diffusion metrics are developmentally sensitive markers of water directionality, the presence of crossing fibers makes it difficult to distill the exact properties captured by DTI.

Second, although we measured associations between individual differences in pubertal development and WM properties over the course of a decade, we only utilized diffusion imaging *after* puberty. Only measurements of WM collected within-individual repeatedly over time can discern whether WM development itself is hastened, protracted, or altered in conjunction with time-varying pubertal trajectories. Tractography may better account for within-person neuroanatomical tract differences, rather than TBSS, which relies on normalization of WM structure across individuals (Bach et al., 2014).

Third, we did not directly assay pubertal hormones or use physical exam to determine pubertal maturation, but rather relied on girls' self-reported indicators of their pubertal development. Given that changes in pubertal hormones during adolescence directly target brain regions, it is likely that circulation of hormones early on in late childhood and/or early adolescence may influence the timing and pace of secretion once puberty commences. Combined neuroimaging and direct measures of pubertal hormones, as well as additional informants (e.g., parents), are needed to elucidate connections between WM development and the timing or onset of puberty at the biological-systems level.

Fourth, while it could be that pubertal tempo does not affect neurobiological changes in the same way that behavioral outcomes are affected, there is no consensus on the measurement and modeling of tempo (Beltz et al., 2014). The Gompertz model assumes that tempo is rapid at the inflection point (37% through the curve), which is where the age of our pubertal timing measure was estimated. Other models of nonlinear growth may better describe differences in pubertal trajectories that contribute to variations in brain development. The least recommended approach to examining puberty is via a linear model, which assumes exponential growth, though the association between any type of model-based pubertal tempo and brain measures have not previously been examined. Studies with larger sample sizes would potentially benefit from the use of latent class growth analysis, in which the shapes of trajectories could be estimated freely and examined in relation to brain development. While the current study showed considerable variation in brain WM microstructure that could be attributed to individual differences in pubertal development, it is not possible to disentangle the contributions of the three pubertal dimensions. Separating pubertal status, timing, and tempo is complex (Mendle et al., 2011), particularly considering that age 9 status is a snapshot of pubertal development, timing is an estimation of the age at which individuals approach a certain point on a curve, and tempo is a measure of the rate of intra-individual change. Additionally, although many of our results were significant at the p value of .01, we did not conduct a formal multiple comparisons correction and caution the reader in their interpretation of the results.

Finally, the current study benefited from the use of a prospective, longitudinal cohort of girls, allowing physical changes from late childhood to late adolescence to be captured in a sex-specific manner. Given behavioral studies emphasizing the role of pubertal timing and tempo on psychosocial outcomes among girls, the approach of examining only girls seems appropriate. However, it is unclear whether our findings of the role of early differences in pubertal status and pubertal timing on later WM properties might be similar in males. Larger longitudinal cohort studies including both boys and girls might examine how dimensions of pubertal development similarly or differently relate to brain development across the sexes. Nevertheless, our findings reinforce the importance of studying sexes separately when examining the association between pubertal maturation and the developing brain. Our study participants were also from lower socioeconomic backgrounds, with many families reporting receipt of public assistance. Additionally, a high proportion of girls were African American. These factors limit the generalizability of the findings to other adolescent samples of varying demographics and socioeconomic backgrounds.

4.2. Future directions

Future studies that directly assay hormones, include longitudinal neuroimaging, and assess behaviors, emotions, and cognition are needed to determine when and how individual differences in pubertal development influence neuroplasticity and emotional health. Further, the use of methods that afford more fine-grained microstructural specificity is needed to understand the underlying mechanisms of WM maturation as they relate to puberty. Multiple fiber populations often traverse the same voxel (crossing fibers), making it difficult to infer what features of WM organization are being captured by FA, MD, and RD. Fixel-based analysis (FBA) is a novel method used to characterize microscopic fiber density, as well as macroscopic properties of fiber-bundle morphology. This method provides insight about fiber populations within voxels (fixels), and has clearer interpretability compared to voxel-averaged measures of FA and MD (Raffelt et al., 2017). Neurite orientation dispersion and density imaging (NODDI) is another technique that could be used to uncover other aspects of WM tissue microstructure in relation to pubertal development. By measuring diffusion gradients of varying strengths, NODDI is used to quantify axon and dendrite tissue (neurite) density and neurite dispersion (Zhang et al., 2012). With the use of other imaging techniques such as NODDI and FBA, we may begin to understand the underlying mechanisms of WM maturation due to pubertal processes, and avoid speculating about differences in DTI metrics.

5. Conclusions

Our findings demonstrate that pubertal status early on (age 9) and pubertal timing are important features in determining WM organization at age 19. Our results underscore the need to consider individual differences in dimensions of puberty early in development when characterizing development of the brain across adolescence. We showed that more advanced gonadal-based physical maturation at age 9, was associated with higher FA in frontotemporal regions and lower MD and RD in WM regions previously shown to be associated with concurrent pubertal status. Additionally, we found that earlier pubertal timing was associated with lower MD in the left anterior cingulum, a WM bundle connecting limbic brain regions essential to emotion processing and memory formation. Our findings suggest that aspects of pubertal maturation (i.e., early status and timing) have lasting connections with the young adult brain, where earlier physical maturation may yield speeded changes in WM microstructure.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.07.050.

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