Adrenarchal hormone-related development of white matter during late childhood

Marjolein E.A. Barendse\(^a,b,*,\) Julian G. Simmons\(^a,c\), Robert E. Smith\(^d,e\), Marc L. Seal\(^f,g\), Sarah Whittle\(^a,c\)

\(^a\) Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Parkville, VIC 3052, Australia
\(^b\) Department of Psychology, University of Oregon, 1440 Franklin Boulevard, Eugene, OR 97401, USA
\(^c\) Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, VIC 3052, Australia
\(^d\) The Florey Institute of Neuroscience and Mental Health, Heidelberg, VIC 3081, Australia
\(^e\) The Florey Department of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC 3052, Australia
\(^f\) Department of Paediatrics, The University of Melbourne, Parkville, VIC 3052, Australia
\(^g\) Developmental Imaging, Murdoch Children’s Research Institute, Parkville, 3052 VIC, Australia

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**Abstract**

The aim of the current study was to longitudinally examine how adrenarchal hormones influence the development of white matter structure from age 8.5 to 10 years. Participants were 120 children (66 female; mean age 8.45 years at Time 1 and 9.97 years at Time 2) who completed two diffusion-weighted imaging scans 1.5 years apart. Morning saliva samples were taken at both assessment time points to measure levels of dehydroepiandrosterone (DHEA), its sulphate (DHEAS), and testosterone. Pixel-based analysis was performed to examine how changes in white matter fibre density (FD) and cross-section (FC) over time were associated with initial levels of hormones, and changes in hormone levels over time. Both FD and FC increased over time in a wide range of white matter tracts. Increases in testosterone over time were related to relatively weaker increases in FC in the inferior fronto-occipital fasciculus. Levels and change in DHEA and DHEAS were not related to FD or FC changes. The results demonstrated development of white matter fibre density and cross-section from age 8.5 to 10 years. Changes in adrenarcheal hormone levels showed limited, localized associations with development of white matter FC. Future research should examine the relevance of adrenarcheal hormone-related white matter development for cognitive functioning; as well as directly compare analysis techniques of white matter structure.

1. Introduction

White matter development continues throughout childhood and adolescence, with well-established increases in volume and changes in microstructure (e.g. fractional anisotropy [FA] and mean diffusivity [MD]) with age (Lenroot et al., 2007; Simmonds et al., 2014). Pubertal processes are thought to influence this development, with the majority of relevant studies demonstrating positive associations between hormonal and physical markers of pubertal maturation and white matter volume or microstructure (Chahal et al., 2018; Herting et al., 2012, 2017; Menzies et al., 2015; Peper et al., 2008; Perrin et al., 2008).

However, only two studies to our knowledge have examined the association between puberty and white matter development longitudinally, and results have been inconsistent. Herting and colleagues (2017) showed that physical signs of puberty (based on Petersen’s Pubertal Development Scale [PDS; (Petersen et al., 1988]) in participants 10–18 years of age predicted changes in FA in the thalamus, superior frontal gyrus, precentral gyrus, genu of the corpus callosum, and superior corona radiata. Sex-specific effects were evident, such that, for example, increases in pubertal development were associated with increases in FA in superior frontal and precentral gyrus white matter in boys, but decreases in FA in girls. Genc et al. (2018), however, found no associations between changes on the PDS and development of fibre density or fibre cross-section over a period of 16 months in 9- to 13-year-olds. The inconsistency in these findings could be due to differences in the age ranges or differences in the derived measures of white matter microstructure, which might provide information on different aspects of white matter development (some of which might be more strongly associated with the physical signs of puberty than others).

Compared to the literature on physical pubertal development described above, there is limited research on how changes in pubertal hormones relate to white matter structure. Further, there is limited re-
search focusing on the adrenarcheal period, an earlier phase of puberty that starts around age 7–8 years (Campbell, 2006; Reiter et al., 1977). In contrast to gonadarche, there are very few physical signs of adrenarche, but this developmental phase does involve clear hormonal changes: mainly increases in the levels of dehydroepiandrosterone (DHEA), its sulphate (DHEAS), and testosterone. DHEA and DHEAS are neurosteroids (Maninger et al., 2009), and all three hormones have been found to show associations with brain structure and function during adrenarche (Barendse, Simmons, Byrne, Patton, et al., 2018; Nguyen et al., 2013; Whittle et al., 2015). Specifically regarding white matter, we have previously found that higher levels of adrenarchal hormones (controlling for age) are linked to lower frontal white matter volume (Klauser et al., 2015) as well as higher MD across many white matter tracts (Barendse, Simmons, Byrne, Seal, et al., 2018). These findings are in contrast with the results of the majority of studies relating gonadarcheal development and white matter properties, suggesting hormonal changes underlying adrenarche might have distinct effects on white matter compared to those underlying gonadarche. However, both of these studies were cross-sectional, and no longitudinal research on white matter development in relation to adrenarche, specifically, has been done to our knowledge.

Considering the importance of longitudinal research for differentiating chronological age from pubertal effects on brain development (Vijayakumar et al., 2018), and for better estimating the direction of effects, the aim of the current study was to longitudinally examine how initial levels of adrenarchal hormones, as well as changes in levels of these hormones, are associated with the development of white matter structure during the late childhood/adrenarchal period. Based on previous cross-sectional findings regarding DHEA (Barendse, et al., 2018b), DHEAS (Barendse, et al., 2018b) and testosterone (Herting et al., 2012), we expected that higher initial levels of DHEA, but not DHEAS, would be related to less change in white matter structure across two time-points, whereas higher levels of testosterone would be positively related to change in white matter structure. The association between changes in hormone levels and changes in white matter structure was examined as an exploratory aim because of the lack of previous research regarding changes in adrenarchal hormones. Given long-held speculation that hormonal changes likely contribute to structural brain development (Giedd et al., 1997), which remains an open question (Herting and Sowell, 2017), this analysis could provide an important contribution to understanding how individual differences in the trajectory of pubertal development associate with white matter development.

Recent methodological advancements in white matter research have led to a shift towards measures that are closer to a physiological process, and overcome common methodological issues, such as crossing fibres (Tournier et al., 2008). Fixel-based analysis (FBA) is a framework for characterizing white matter changes that allows inferences on the specific fibre bundle implicated within crossing-fibre regions, thus providing more valid indices of white matter structure (Raffelt et al., 2017). Here we utilized this framework to interrogate two quantitative measures in whole-brain analyses: fibre density (FD), a measure of microscopic white matter fibre axon density; and fibre cross-section (FC), a measure of macroscopic morphological fibre bundle changes. To aid comparison with the existing literature, we have provided results for FA and MD in the Supplement.

2. Material and methods

2.1. Participants

Participants were recruited from Melbourne metropolitan areas classified by the Australian Bureau of Statistics as falling within the lower tertile of socioeconomic status (based on the 2011 national Australian population census). This approach counteracted the self-selection bias that is often present in community samples and hence led to a broadly generalizable sample of families with a wide range of socioeconomic status, as demonstrated by the sample’s Australian Socioeconomic Index 2006 score ranging from 24 to 100 (M=60.20, SD=20.17) at the first time point of the study. Children were between 8 and 9.25 years old at the time of the first assessment, and were followed up approximately 1.5 years later. Participants were excluded if they had a history of developmental or intellectual disorder, claustrophobia, non-removable ferrous metals in their body, or if they used amphetamine-based medication in the month before the MRI scan (because this has been associated with alterations in brain structure and function (de Luís-García et al., 2015)). The study was approved by the University of Melbourne Human Research Ethics Office (#1339904). Participants provided verbal assent, with a parent/guardian providing written consent. Full details of the design, recruitment strategy, and measures can be found in the study protocol (Simmons et al., 2017).

163 children and their parents agreed to participate in the study, of which 142 (87%) returned for the second assessment. 122 participants completed a diffusion-weighted imaging (DWI) scan at both time points. One participant was excluded because of motion-related artefacts, and another because of amphetamine-based medication use at the time of the second assessment, leaving 120 participants in the final sample (66 female), with age 8.45±0.33 years at Time 1 (T1) and age 9.97±0.35 years at Time 2 (T2). The time between assessments was 1.53±0.11 years (range 1.40–1.93). The final cohort for analyses involving both DWI and hormonal data included 110 participants: 8 were excluded due to saliva samples being collected >45 minutes after waking; 2 were excluded due to having no hormone data available. Further participants were excluded from analyses involving DHEAS: n=2 for analyses involving T1 levels, and n=5 for analyses involving changes between T1 and T2 levels, due to missing flow rate information (see Saliva collection and Processing). There were no differences in age, sex distribution, or hormone levels, between those in the final cohort and excluded participants (all p>0.25).

2.2. Saliva collection and processing

Children, with the help of a parent/guardian, were asked to collect a saliva sample on two consecutive days, through passive drool immediately after waking, and prior to the consumption of food or teeth brushing. Children were asked to record the time it took to collect the sample with a stopwatch, and to write down the time of waking and the time they started collecting the sample. Parents were given the same instructions so they could assist their child. Saliva samples were excluded from hormone analyses if they were collected >45 min after waking. The average of the samples on the two consecutive days was used in analyses.

Saliva samples from both assessment time points were assayed for testosterone, DHEA and DHEAS using Salimetrics ELISA kits (www.salimetrics.com). At T1, intraassay coefficients of variation (CVs) were 8.17%, 9.03%, and 7.82%, respectively, and interassay CVs were 10.47%, 11.76%, and 13.77% respectively. At T2, intraassay CVs were 6.57%, 10.71%, and 10.51% respectively, and interassay CVs 14.79%, 10.76%, and 9.59% respectively. In cases where the level of a hormone in the saliva was undetectably low, the midline of the undetectable range for that hormone was imputed, which occurred for 7.1% of the Time 1 data and 2.7% of the Time 2 data. Imputation is the preferred method to deal with this issue because excluding samples with undetectable levels would create a bias towards (participants with) higher hormone levels. Having a subset of participants with undetectably low hormone levels is quite common in this age range (Belsky et al., 2015; Neufang et al., 2009).

Levels of DHEAS were corrected for flow rate (in ml/s). We examined both initial hormone levels (levels at T1), as well as changes in hormone levels from T1 to T2. Any outliers (–3.3<r<3) were winsorized to 1% above/below the next highest/lowest value. Nine outliers were winsorized in total (two each on change in DHEA, T1 testosterone, and T1 DHEAS; 1 each on T1 DHEA, change in testosterone, and change in
DHEAS). Finally, T1 hormone levels were log-transformed to yield an approximately Gaussian distribution.

Body Mass Index (BMI) was included as a covariate in the hormone analyses as it has been linked to levels of adrenal hormones around adrenarche and could otherwise confound inference on effects of the hormones (Ong et al., 2004). Height and weight of each participant were measured by a research assistant at both time points to calculate BMI (see protocol; Simmonds et al., 2017). A BMI z-score was calculated based on population norms from the World Health Organization (http://www.who.int/growthref/who2007_bmi_for_age/en/) to obtain sex- and age-specific values, and an average of the z-scores of the two time points was used as a covariate in analyses.

2.3. Diffusion-weighted imaging protocol

All DWI images were acquired by a 3T Siemens Tim Trio scanner at the Royal Children’s Hospital in Melbourne. Participants were prepared for scanning by using a mock scan procedure and watched a movie during DWI imaging, which has been found to reduce head motion when scanning children (Greene et al., 2018). Scanning parameters at both time points were as follows: TR = 8500 ms, TE = 112 ms, FOV = 22.5 cm, matrix size 98 x 98, 58 slices with voxel dimensions = 2.3 mm³, EPI factor=98. The sequence consisted of diffusion-weighted scans in 45 gradient directions at b = 3000 s/mm², interspersed with five non-diffusion-weighted scans (b = 0 s/mm²), and followed by a pair of b=0 volumes with opposing phase encoding directions (anterior-posterior and posterior-anterior) for the purpose of estimation of B0 field offsets (Andersson et al., 2003).

2.4. DWI pre-processing and statistical analyses

Firstly, scans were visually checked for gross movement, ghosting and other artifacts; one participant was removed as mentioned under Participants. Images were denoised (Verhaart et al., 2016), and then corrected for EPI induced susceptibility artifacts, eddy current distortions, signal dropout (Andersson et al., 2016), and for inter- and intra-volume (Andersson et al., 2017) head movement using the eddy tool, provided as part of FMRIB Software Library (FSL)v5.0.11 (Andersson and Sotiropoulos, 2016). Movement in all scans was measured by calculating the mean relative frame-wise displacement between the b=0 images (as in Roalf et al., 2016), and was comparable between the two time points (T1 M=0.50, SD=0.41; T2 M=0.45, SD=0.36; paired t (119)=1.10, p=.27).

We performed fixed-effect analysis (FBA) on the preprocessed DWI scans using the recommended pipeline in MRtrix3 version 3.0_RC2 (Raffelt et al., 2017). This included: upsampling the data to a voxel size of 1.25mm³; estimating fibre orientation distributions (FODs) for each scan (Tournier et al., 2007) using average response function across the sample (Raffelt et al., 2012), and creating a study-specific FOD template (Raffelt et al., 2011) from a random subset of scans. To be able to conduct unbiased longitudinal FBA analyses, the template was based on an equal number of scans (20) from both time points. Each individual’s FOD image was then registered to the template and the transformed FOD within each template space voxel was segmented (Smith et al., 2013) to produce a set of discrete fixels. Fibre density (FD) and fibre cross-section (FC) metrics were calculated as in Raffelt et al. (2017): FD refers to the volume of restricted water in a given direction in a voxel and thereby reflects the density of the fibres in a bundle; FC reflects the size of a fibre bundle cross-section relative to the template. In accordance with the recommended pipeline, FC metrics were log-transformed. For each of the two metrics, the change in value between the two time points was computed for each fixel, further on referred to as ∆FD and ∆FC.

Statistical inference on ∆FD and ∆FC was conducted using Connectivity-based Fixed Enhancement (CFE) (Raffelt et al., 2015), which utilizes whole-brain tractography on the FOD template to specifically enhance statistical measures along white matter pathways. Tractography on the FOD template was conducted with the following parameters: 22.5 degree angle threshold, 1.15mm step size, 0.1 FOD amplitude cut-off, 10mm minimum and 250mm maximum track length. One sample t-tests were performed on ∆FD and ∆FC across the whole brain, controlling for T1 age and sex, to examine changes in metric values between the two time points. Results were generated using 5000 permutations and whole-brain corrected at family wise error (FWE) corrected p<.05. Post-hoc analyses that included the interval between the two time points as a covariate led to consistent results (not shown). Note that we did not control for whole brain volume since this might remove relevant variance, and the majority of longitudinal studies on structural brain development do not control for this (Vijayakumar et al., 2017). In addition, associations between fixed metric changes and the hormone variables (both T1 levels, and changes in levels from T1 to T2) were tested with whole-brain linear regression, controlling for age at T1, sex, and BMI z-score. Results were again generated using 5000 permutations. These analyses were corrected for the number of predictor variables tested. The average correlation between the six hormone variables (initial levels and changes for three hormones) was r=.27. Bonferroni correction taking into account this correlation (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm) led to an adjusted FWE-corrected p-threshold of .0135.

Further, we explored differences between the sexes in ∆FD and ∆FC (with two-sample t-tests) and interactions between the hormone variables (both T1, and change from T1 to T2) and sex. Finally, although FC and FD were theoretically chosen as measures of white matter structure in this manuscript (as explained in the Introduction), additional analyses examining the same association in relation to FA and MD are reported in the Supplement to benefit comparisons with the existing literature.

Labelling of the tracts where significant findings occurred, was based on the JHU White Matter Tractography atlas.

3. Results

Demographic information and means, standard deviations, and statistical differences in key variables between the two time points are presented in Table 1. DHEA and DHEAS increased significantly over time in the whole sample, whereas testosterone did not change from T1 to T2. Regardless of group-level change, there were marked individual differences in change (see Fig. 1). See Table 2 for correlations between the (changes in) hormone levels and Supplementary Table S1 for demographic data and hormone levels by sex.

3.1. Change in fibre density and fibre cross-section over time

Both FD and FC significantly increased over time in various white matter regions (see Fig. 2). Increases in FD were found in the forceps major and minor (also known as the splenium and genu of the corpus callosum), the cingulum bundles, the right inferior fronto-occipital fasciculus (IFOF), and the corticospinal tracts (peak t=20.48, p_{FWE}<.001; across all significant fixels, the mean increase was 4.17%, SD=2.20). Significant increases in FC were shown across a wide range of major white matter tracts (peak t=26.66, p_{FWE}<.001; the mean increase across all
Table 2

Correlations between hormone variables.

| DHEA T1 | DHEAS T1 | Testosterone T1 | DHEA T2 | DHEAS T2 | Testosterone T2 | DHEA change | DHEAS change | Testosterone change |
|---------|----------|-----------------|---------|----------|-----------------|-------------|--------------|---------------------|
| DHEA T1 | 1        | .68             | .70     | .17      | .69             | .12         | −.01         | .17                 |
| DHEAS T1| 1        | .57             | .54     | .42      | .57             | .12         | .09          | .07                 |
| Testosterone T1 | 1 | .46 | .08 | .63 | −.02 | −.06 | −.24 |
| DHEA T2 | 1        | .42             | .75     | .66      | .26             | .51         |              |                     |
| DHEAS T2 | 1       | .27             | .36     | .86      | .31             |             |              |                     |
| Testosterone T2 | 1 | .44 | .13 | .55 |
| DHEA change | 1 | .36 | .61 |
| DHEAS change | 1 | .28 |

Pearson’s r correlations shown; correlations with p<.05 are in bold. DHEA=dehydroepiandrosterone; DHEAS=dehydroepiandrosterone-sulphate; T1=Time 1; T2=Time 2.

Fig. 2. Significant increases in fibre density (left) and fibre cross-section (right) between Time 1 and Time 2 of the study. Streamlines were cropped from the template tractogram to show only points that correspond to significant fixes (p<.05) and are presented on top of the study-specific template. The left side of each panel shows the developing tracts color-coded by direction (red is left-right, green is anterior-posterior, and blue is superior-inferior). The right half of each panel is color-coded by effect size (in arbitrary units).

4. Discussion

The current study demonstrated increases in both FD and FC in a wide range of white matter tracts from age 8.5 to 10 years. The increases in FD and FC are consistent with a recent study (Genc et al., 2018), and are in line with the literature on development of white matter volume and FA with age (Lenroot et al., 2007; Simmonds et al., 2014). Changes were found in commissural, projection, as well as association tracts; but the strongest effects were found in the posterior half of the brain and in earlier developing pathways such as the corticospinal tract. This may be reflective of the age range studied, as projection tracts and tracts in the posterior parts of the brain develop relatively early, whereas tracts that showed no changes in the current study (e.g. the uncinate fasciculus) are known to develop into late adolescence and young adulthood (Asato et al., 2010; Simmonds et al., 2014).

In increases in the FD metric reflect an increase in the proportion of restricted water in a voxel in the direction of the fibre (Raffelt et al., 2012). The FC metric is indicative of the size or cross-section of a bundle of fibres. Increases in both over time, as demonstrated here, have been suggested to reflect increases in the number of axons and/or axon diameter or calibre (Genc et al., 2018; Raffelt et al., 2017). Growing axon calibre has been described previously as an important contributor to continued white matter development across childhood and adolescence – alongside myelination, which can both improve the speed of signal transmission across the axon (Paus, 2010). However, crossing-fibre diffusion models like FBA are still only reconstructions of the diffusion signal, and therefore we cannot say with any certainty which biological processes underlie changes in FD and FC. Also, the neurodevelopmental bases and functional implications of more extensive FC as compared to FD changes require further investigation.

Further, the current study was the first longitudinal study relating (adrenarcheal) hormone levels to white matter development. We found that changes in testosterone over time (from ages 8 to 10) were negatively related to changes in FC in the inferior fronto-occipital fasciculus. Since the overall trend was an increase in FC over time, those with more positive changes (increases) in testosterone showed weakened increases in FC in this tract. The direction of this finding does not completely align...
with the predominant view in the literature that hormonal changes during puberty support or contribute to white matter development, or that more advanced pubertal maturation is associated with more advanced white matter development (Herting et al., 2012, 2017; Menzies et al., 2015; Perrin et al., 2008). However, not all previous studies have supported this view (Herting et al., 2017; Peper et al., 2015) and it is solely based on maturation during gonadarche. Specifically for testosterone, previous research suggests positive associations with white matter volume (Vijayakumar et al., 2018) and axon calibre (Hervé et al., 2009; Pangelinan et al., 2016; Paus, 2010), particularly in males. Based on this research, we would expect a positive link between testosterone and ΔFC and ΔFD. However, the studies mentioned above were all focused on adolescence, when much higher levels of (gonadal) testosterone are present, particularly in boys. The absence of an association in females in previous studies suggests that these effects might not be present at lower overall levels of testosterone, or at lower rates of change of this hormone. This could explain the negative association between change in testosterone and ΔFC and the absence of an association with ΔFD found here.

Since there was little variation in the time between assessments, another possible explanation is that a stronger increase in testosterone over time could reflect relatively fast maturation or high tempo of adrenarche. With this interpretation in mind, relatively fast progression through adrenarche (T1 to T2) was found to relate to weakened FC development. It should be noted that the study was not designed to measure tempo of adrenarche, and therefore this is only a speculative interpretation of the meaning of our findings, which should be explicitly tested in future research. Tempo of adrenarche has received no attention in the literature, but during gonadarche tempo is considered an important indicator of individual functioning, with faster progression generally linked to poorer developmental/psychological outcomes (Mendle, 2014).

The only two studies that focused specifically on hormone levels during adrenarche in relation to white matter structure demonstrated that relatively high levels of DHEA were associated with lower frontal white matter volume (Klausner et al., 2015) and higher mean diffusivity across many white matter tracts (Barendse et al., 2018). Since both studies included a narrow age range and controlled for age, the findings were interpreted as an effect of adrenarcheal timing. Considering the similar methods used in the current manuscript (i.e., narrow age range in addition to statistical age correction), combined with a relatively large sample and longitudinal set up, our negative findings could be interpreted as no substantial association between timing of adrenarche and FD or FC development. It should be noted that, before Bonferroni correction, there were significant associations between initial levels of testosterone and change in FC in the forceps major. Further research on the relevance of adrenarcheal timing for longitudinal white matter development, potentially over a longer time span, is therefore warranted.

These negative findings are not completely in line with our hypotheses, or with the findings of previous cross-sectional studies as described above (Barendse et al., 2018b; Klauser et al., 2015). The different models and quantitative parameters that previous studies used to analyse the white matter compared to the current manuscript may assess different aspects of white matter development (e.g. increases in axon diameter, myelination, reorganization of glial cells surrounding the axons), which could contribute to differences in findings. This is evident in the limited overlap between the current findings for FC and those for FA reported in the Supplementary Materials. It is also illustrated by the difference in findings between the two studies described in the introduction that related physical signs of puberty to either FA or fibre density and cross-section (Genc et al., 2018; Herting et al., 2017). It should be noted that our scanning sequence was not optimized for DTI-metrics such as FA, so direct comparisons between the FC and FA findings should be considered with caution. The discrepancies in findings between different measures of white matter microstructure imply that careful consideration of which analysis technique to apply is important, and warrants direct comparison of different measures of white matter microstructure in developmental samples, as well as the use of imaging techniques that are specific to only one aspect of white matter development.

Associations of FC with testosterone were limited to the posterior half of the IFOF (and before Bonferroni multiple comparisons correction the CC-splenium). Previous research demonstrated that only this tract matures (based on radial diffusivity) during the early stages of pubertal development, while other tracts showed maturation further in gonadarche (Asato et al., 2010). Together with the current findings, this suggests that hormonal processes in early puberty might be particularly relevant to the development of the IFOF. The IFOF connects occipital and temporal areas to the frontal cortex and is thought to be involved in several cognitive processes, including language processing (Bajada et al., 2015) and visuospatial working memory (Krogstad et al., 2018). Although we did not assess cognitive outcomes in the current study, this might suggest that individual variability in testosterone change has an impact on white matter development underlying cognitive abilities. A recent study demonstrated that testosterone-related prefrontal-hippocampal structural covariance was negatively related to executive functioning in males age 6–22 (Nguyen et al., 2017). This highlights the potential relevance of testosterone-related brain development for cognitive functioning, which requires future examination with regard to white matter development.

4.1. Limitations and directions for future research

The reliability of fibre density and cross-section are not yet known, since fixel-based analysis is a relatively new technique. However, our findings of increases in fibre density and cross-section with development are consistent with a previous study (Genc et al., 2018), mak-
ing it more likely that this technique is able to detect true change over time. Nonetheless, examination of the reliability of this technique is warranted.

Further, we speculated that the initial levels and temporal changes in testosterone could be interpreted as timing and tempo of adrenarche, respectively. To thoroughly examine the impact of timing and tempo of adrenarche on white matter development, however, it would be preferable to use three or more time points of hormone assess and apply linear mixed models or growth curve modelling to establish individual indicators of the timing and tempo of hormonal change.

Also, in the current study we did not examine how the changes in adrenarche hormones and fibre density and cross-section development relate to cognitive development. Considering the substantial language and other cognitive development taking place during late childhood, as well as the centrality of cognition-related white matter tracts as discussed above, it is possible that the associations found between testosterone and white matter development impact cognition. Future research should thus establish the relevance of adrenarche hormone-related white matter development for cognitive functioning.

4.2. Conclusion

The current study demonstrated widespread development of white matter fibre density and cross-section from age 8.5 to 10 years. We found only limited relevance of adrenarche hormone changes for white matter development, specifically in the inferior fronto-occipital fasciculus, which we speculated may reflect associations of tempo of adrenarche with white matter development. However, our findings need to be replicated using more than two hormonal assessment time points and measurement of white matter development over a wider time span. Comparing the findings in the main manuscript to FA and MD results in the Supplement showed that hormone-related changes depend on the measure of white matter structure, but a more direct comparison of analysis techniques is warranted. Also, as a next step it will be important to examine the relevance of adrenarche hormone-related white matter development for cognition.

Author contributions

Marjoline Barendse: Conceptualization, Formal analysis, Writing – Original Draft, Writing – Review and editing, Supervision, Funding acquisition. Robert Smith: Software, Resources, Writing – Review and editing. Marc Seal: Conceptualization, Writing – Review and editing, Funding acquisition. Sarah Whittle: Conceptualization, Writing – Review and editing, Supervision, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117320.
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