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Unraveling age, puberty and testosterone effects on subcortical brain development across adolescence

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ABSTRACT

The onset of adolescence in humans is marked by hormonal changes that give rise to secondary sexual characteristics, noted as puberty. It has, however, proven challenging to unravel to what extent pubertal changes may have organizing effects on the brain beyond chronological age, as reported in animal studies. The present longitudinal study aimed to characterize the unique effects of age and puberty on subcortical brain volumes and included three waves of data collection at two-year intervals and 680 T1-weighted MRI scans of 271 participants (54% females) aged between 8 and 29 years old. Generalized additive mixed model procedures were used to assess the effects of age, self-report pubertal status and testosterone level on basal ganglia, thalamus, hippocampus, amygdala and cerebellum gray matter volumes. We observed age-related increases in putamen and pallidum volumes, and decreases in accumbens and thalamus volumes, all show larger volumes in boys than girls. Only the cerebellum showed an interaction effect of age by sex, such that males showed prolonged increases in cerebellar volume than females. Next, we showed that changes in self-report puberty status better described developmental change than chronological age for most structures in males, and for caudate, pallidum and hippocampal volumes in females. Furthermore, changes in testosterone level were related to development of pallidum, accumbens, hippocampus and amygdala volumes in males and caudate and hippocampal volumes in females. The modeling approach of the present study allowed us to characterize the complex interactions between chronological age and pubertal maturational changes, and the findings indicate puberty unique changes in brain structure that are sex specific.

1. Introduction

Adolescence, the transitional period between childhood and adulthood, is characterized by substantial changes in brain structure and activity, particularly in regions that have been indicated to play key roles in adolescent specific behaviors (Mills et al., 2016; Braams et al., 2015). The onset of adolescence is delineated by puberty, characterized by hormonal changes that give rise to secondary sexual characteristics (Shirtcliff et al., 2009). Several studies showed associations between subcortical brain development and pubertal characteristics (Herting et al., 2015; Bramen et al., 2011; Blanton et al., 2012; Satterthwaite et al., 2014; Goddings et al., 2014, but see Koolschijn et al. (2014)). Additionally, animal studies suggest that testosterone has modulating effects on brain development that are puberty specific (Schulz and Sisk, 2016), it remains an open question to what extent puberty in humans may be another period during which gonadal hormones may affect human brain development. The present longitudinal study aimed to address this issue by characterizing the specific role of age-related and puberty-related development on change in subcortical brain volumes in a community sample of adolescents and young adults.

Several lines of research suggest that puberty may represent a (second) reorganizational period in the brain (Juraska and Willing, 2017). Animal research has provided initial direct evidence that puberty represents a critical period during which hormones may promote organizing effects on brain structure. For example, experienced deprivation of testosterone in pubertal hamsters resulted in structural alterations in amygdala volume in adulthood, independent of adult levels of testosterone (De Lorme et al., 2012). Furthermore, Zehr et al. (2006) showed that synaptic pruning in the medial amygdala was associated with pubertal status in male Syrian hamsters. Moreover, pubertal exposure to androgens in male rates was related to increases in spine density of amygdala and hippocampal structures (Cunningham et al.,

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2007). In addition, it was observed that exposure of gondal hormones during puberty was critical for the sensitivity of limbic regions to steroid hormones in adulthood: androgen receptor density was increased following prepubertal (but not postpubertal) castration in male Syrian hamsters (Romeo et al., 2000). Also in female species, puberty specific effects on brain development were observed. For example, prepubertal ovariectomy in female rats resulted in neural overproduction in the frontal cortex (Koss et al., 2015), while adult ovariectomy did not (Chisholm et al., 2012). These studies support a causal role for puberty on developmental brain changes.

Although causal relations between puberty and brain development can not be exerted in humans, there are several lines of evidence that indicate that puberty may mark a sensitive period in brain development in humans (Peper et al., 2011). First, several subcortical structures showed volume changes that emerge or peak in the pubertal age range (e.g. Ostby et al., 2009; Koolschijn and Crone, 2013; Wierenga et al., 2014), however, there are inconsistencies regarding the timing and directionality of these developmental trajectories (Herting et al., 2018). This highlights the importance of studying these effects in a large single cohort, covering a wide age range and including more than 2 time points. Second, studies have reported that males show a delay in peak volume compared to females (Lenroot et al., 2007), which has been suggested to correspond to sexual dimorphic trajectories in pubertal maturation. Third, a puberty related peak in functional activity (e.g nucleus accumbens) has been related to adolescent characteristic behaviors (e.g. heightened reward sensitivity) (Galvan et al., 2006; Braams et al., 2014). These peaks in functional activity showed to be related to testosterone (Braams et al., 2015).

Most studies investigating pubertal effects on subcortical brain development in humans have been cross-sectional. In one study, pubertal maturation was associated with grey matter volumes in the medial temporal lobe (MTL), yet differently for boys and girls: more advanced pubertal maturation was associated with larger hippocampal volume in boys, but with smaller hippocampal volume in girls (Bramen et al., 2011). Cross-sectional studies also demonstrate a relation between pubertal maturation and hippocampal volume, yet the direction of the effect remains inconclusive (Hu et al., 2013; Neufang et al., 2009; Satterthwaite et al., 2014). Cross-sectional studies that focused on effects of testosterone on subcortical brain development have also shown mixed results. Both positive as well as negative associations between amygdala volume and testosterone were observed (Bramen et al., 2011; Neufang et al., 2009). In addition, caudate volume and thalamus volume did not show significant relations with pubertal measures (Bramen et al., 2011). However, these cross-sectional studies evaluated only a limited number of subcortical structures and do not take into account the inter individual variation in brain and pubertal development, for which longitudinal studies designs are crucial.

To date, there are only a few longitudinal studies available in humans that assessed puberty-related associations on subcortical brain development (for a review, see Herting and Sowell (2017)). Goddings et al. (2014) showed that increase in pubertal stage was related to subcortical brain development; a positive relation with hippocampus and amygdala volume and a negative relation with caudate, putamen and nucleus accumbens volume. Another longitudinal study only found this longitudinal relation between pubertal stage and caudate volume (Herting et al., 2015). The latter study also observed that decreases in amygdala and caudate volumes were associated with increases in testosterone levels. These findings suggest that pubertal development may accelerate typical developmental trajectories. One difficulty with these prior studies concerns the collinearity between predictors (age, self-report puberty and sex hormones all increase over time). Our study aimed to overcome these challenges by assessing the effect of individual differences in the onset and change in pubertal measures on subcortical brain development. The inclusion of 3-wave longitudinal assessments of structural brain indices (N = 680 scans), participants in a wide age range (8–29-years) and individual assessment of age, pubertal stage and testosterone levels allowed us to do so.

The goals of this study were to i) delineate chronological age effects on development of subcortical brain volumes, and ii) test effects of pubertal measures, self-report pubertal stage and testosterone level, above and beyond chronological age, and iii) test whether the influence of testosterone is puberty specific. In addition to subcortical regions, we also included cerebellum gray matter in our analyses, given that – in our previous study partly based on the same sample- it was observed to be associated with testosterone (Schutter et al., 2017). Based on the literature we expected to observe regional effects of puberty. We aimed to elucidate the inconsistent findings of pubertal effects on amygdala and hippocampal volumes (Bramen et al., 2011; Herting et al., 2015; Hu et al., 2013; Goddings et al., 2014; Neufang et al., 2009; Peper et al., 2009; Satterthwaite et al., 2014). Furthermore, we hypothesized no effect of puberty on thalamus volume, as no significant effects have been reported (Bramen et al., 2011; Herting et al., 2015). For caudate, putamen, pallidum and accumbens volumes we hypothesized a negative association with pubertal measures (Goddings et al., 2014). We had no hypothesis related to the effect of puberty on cerebellar cortical development, as this has not been investigated previously.

2. Methods

2.1. Participants

The data in the present study are part of a large accelerated longitudinal research project, BrainTime (Braams et al., 2015; Achterberg et al., 2016; Peters and Peper, 2016; van Duijvenvoorde et al., 2016). A total number of 299 participants were enrolled in the study. Magnetic Resonance Imaging (MRI) scans of 271 participants (53% females) aged between 8 and 26 years old at enrollment were included in the present study for further analysis (see Table 1 for demographics). These scans passed the MRI quality control (QC) procedure, which is described in more detail below. Of these participants, 241 had two or more scans (60% females), and 168 participants had three scans (56% females) that passed QC. There was no significant sex difference in age (p-value = 0.103), and the distribution of males and females was similar across the age range (see Fig. A1). Self-report questionnaires were assessed to confirm the absence of neurological, endocrinological, mental health problems or use of psychotropic medication at T1. Written informed consent was obtained from all participants at each time point. For participants younger than 18 years old, additional consent from their parents was acquired. An independent clinical neuroradiologist evaluated all MRI- scans. No gross abnormalities were reported for any of the participants. The study was approved by the Institutional Review Board at Leiden University Medical Center. A financial reimbursement was granted for participation in the study.

Table 1
Subject characteristics.

	Males		Females	
N	127		144	
Age (min-max)	8.01	−28.72	8.01	−26.83
Total number of scans	315		365	
scannr	*N* mean age	(SD)	*N* mean age	(SD)
1	127 14.86	(3.79)	144 14.11	(3.31)
2	114 14.86	(3.77)	127 14.11	(3.24)
3	74 14.86	(4.11)	94 14.11	(3.37)
Height, *mean* (SD)	176.45	(12.23)	167.37	(7.6)
Weight, *mean* (SD)	66.94	(16.78)	61.51	(12.2)
IQ, *mean* (SD)	109.32	(10.96)	109.29	(9.44)
Testosterone, *mean* (SD)	272.58	(167.91)	21.42	(13.81)
PDS, *mean* (SD)	2.53	(0.84)	2.92	(0.79)

N = number of subjects, SD = standard deviation.

2.2. Materials

2.2.1. Pubertal status

Status of physical pubertal maturation was assessed with the Pubertal Development Scale (PDS) for participants under 18 years of age (Petersen et al., 1988). This self-report questionnaire contains questions on secondary sexual characteristics. These characteristics included growth spurt, body hair, changes in the skin, and for males a question about change in voice and facial hair and for females a question about breast development and menarche. The participants were instructed to indicate the developmental stage of each of these physical characteristics on a four-point scale: ranging from (1) has not started to develop, (2) shows first signs of development, (3) shows clear development to (4) has finished developing. The average score on all items was used for further analysis. Data on PDS scores was available for 416 participants under 18 years of age and included 213 subjects at time point one, 143 subjects at time point two and 60 subjects at time point three. Measures that showed a decrease in PDS score with increasing age were discarded, therefore 21 time points were excluded.

2.2.2. Testosterone

Testosterone levels were assessed in morning saliva samples collected by passive drool immediately after waking up and before teeth brushing/eating/drinking. In males and premenarcheal girls, samples were collected on the day of the MRI scanning session. To control for menstrual fluctuations, females who reached menarche collected saliva on the seventh day of their menstrual cycle. Females who used contraceptives with a stopping period also collected saliva on the seventh day of their cycle. These procedures were conducted in order to limit the influence of circadian rhythms, intra-individual daily fluctuations and hormonal fluctuations across the menstrual cycle (Dabbs, 1990). Females who used contraceptives without a stopping period, such as hormonal intrauterine devices, were excluded from assessment.

Testosterone levels were assayed at the Department of Clinical Chemistry at the VU University Medical Center in the Netherlands by isotope dilution—online solidphase extraction liquid chromatography—tandem mass spectrometry (ID-XLC–MS/MS) (Peper et al., 2011). We chose ID-XLC–MS/MS over radioimmunoassay (RIA) as this earlier method is thought to be superior in specificity and variation of hormonal levels (Owen et al., 2016). The lower limit of detection was 4 pmol/L. Data on testosterone measures could be assessed for 89% of the time points in females and 93% of the time points in males. Intra-assay coefficients of variation were 11% and 4% at 10 and 140 pmol/L, respectively, and inter-assay coefficients of variation were 8% and 5% at 31 and 195 pmol/L, respectively and 6.9%, 7.1% and 7.4% at 37, 198 and 984 pmol/L, respectively (de Water et al., 2013). Testosterone levels were available for 296 males (117 time point 1, 107 time point 2 and 72 time point 3) and ranged from 4 to 915 pmol/L. Levels were available for 327 females (131 time point one, 117 time point 2 and 79 time point 3) and ranged from 4 to 90 pmol/L, due to a skewed distribution these values were log transformed for further analysis.

2.2.3. Image acquisition

MRI scans were acquired on a single 3 T Philips Achieva whole body scanner, using a 6 element SENSE receiver head coil (Philips, Best, The Netherlands) at Leiden University Medical Centre. For definition of all brain measures, a whole brain T1-weighted anatomical scan was acquired (TR = 9.8 ms, TE = 4.6 ms, flip angle = 8°, 140 slices, 0.875 mm × 0.875 mm × 1.2 mm, and FOV = 224 × 177 × 168 mm). Scan time for this sequence was 4 min 56 s.

2.2.4. Image processing

MRI scans were analyzed on the local computer network at the Leiden University Medical Center. T1 scans were processed using FreeSurfer 5.3, through which volumetric segmentations were estimated. This software suite is well validated and widely used, it is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). The technical details of the automated reconstruction scheme are described in detail elsewhere (Dale et al., 1999; Fischl et al., 1999a, 1999b, 2002).

In order to reduce within subject scan session variability, a longitudinal stream was developed for FreeSurfer (Reuter and Fischl 2011; Reuter et al., 2012). This method increases repeatability and statistical power (Reuter and Rosas, 2010). All scans were processed using this procedure. This process includes the creation of an unbiased within-subject template space and image ("base") using robust, inverse consistent registration (Reuter and Rosas, 2010). The automated processing steps, including skull stripping, atlas registration and parcellations are next initialized using the common information from the within-subject template. Volumetric estimates of the caudate, putamen, pallidum, accumbens, thalamus, amygdala, hippocampus and cerebellum cortex were extracted and summed across hemispheres and used as regions of interest (ROI).

2.2.5. Quality control

Before quantitative analyses could be performed, output require qualitative inspection (Dewey et al., 2010). Post-processing QC was performed by trained operators trough visual inspection. This inspection focused both on overall image quality and the accuracy of reconstructed segmentations and surfaces. Scans rated poor quality were excluded and the remaining scans from that participants were reprocessed through the longitudinal pipeline to assure the quality of the within-subject template. This QC procedure was repeated until only acceptable scans were included in the longitudinal processing (note that single time points were also processed longitudinally). No manual editing was performed. The QC procedure resulted in the exclusion of 110 scans from 74 participants. The remaining 680 scans were used for further analysis of which demographics can be found in Table 1.

2.3. Statistical analysis

2.3.1. Generalized additive mixed modeling

Accurately modeling neurodevelopment is challenging with parametric models, this for instance assumes that regional age-related changes correspond to linear, quadratic or cubic growth models (Fjell et al., 2010; Alexander-Bloch et al., 2014; Reiss et al., 2014). As such, these models are not optimal to compare groups that show different developmental trajectories (Vijayakumar et al., 2017). Therefore, we used a semi-parametric approach by implementing penalized smoothing splines with generalized additive modeling (Wood, 2004, 2017). These splines have several advantages over polynomial fits: smoothing splines "bend" to data more effectively than polynomials, while at the same time over fitting is prevented by penalization. Furthermore, smooth splines can capture important non-linear growth patterns that are easily missed with polynomials. In addition, spline fits also prevent biased fits at the extreme ranges of the data. Moreover, generalized additive mixed models are well suited for our developmental sample and accelerated longitudinal cohort, as this model accounts for within subject dependence and differences in developmental time points at which participants entered the study (Harezlak et al., 2005; Alexander-Bloch et al., 2014). Finally, these models allow for straightforward hypothesis testing on age-constant trait differences between groups and time-varying states across development.

We conducted six sets of analyses where we examined 1) the effects of age by sex on PDS status and testosterone level; 2) the effects of age by sex on each ROI; 3) the best fitting developmental model by comparing the effects of age to effects of PDS for each ROI; 4) effects of testosterone in each ROI by comparing the best fitting developmental model in analysis three (age or PDS) to a model including testosterone. We additionally tested whether these effects remained after including age at baseline or PDS status at baseline as a covariate to the model and 5) age by PDS group where PDS scores were compared to peers (early or

late) and 6) age by testosterone group where testosterone levels were compared to peers (high or low) in each ROI comparing pre and post puberty. Absolute volumes were used in all analyses, as previous studies show that controlling for intra-cranial volume (ICV) violates important statistical assumptions, including equal variances between groups (Wierenga et al., 2017), and that the covariate should not differ between groups (Miller and Chapman, 2001). Hence co-varying for ICV may differentially affect trajectories of males and females (Mills et al., 2016).

For analysis 1) and 2) we first tested a model with no significant difference between males and females (age only model). More formally, let Age_{ij} denote the age of the i^{th} individual and j^{th} time point. Each measure of interest y_{ij} (brain volume, PDS or testosterone) is modeled as a smooth function s of Age plus a random person effect u_i plus error:

$$y_{ij} = \beta_0 + s_1(Age_{ij}) + u_i + error_{ij}$$

here s is the essential arbitrary smooth function, where the linear combination of piecewise cubic B-spline functions k is set to 4. Here k represents the basis dimensions, k should be set large enough to have enough degrees of freedom to represent the underlying 'truth' reasonably well, but small enough to maintain reasonable computational efficiency. We observed $k = 4$ to be most optimal for our data. We inspected k on a range from 1 to 10 which did not impact on the statistical conclusions to be drawn from a model fit.

Next, we tested whether there was a main effect of sex (main sex effect):

$$y_{ij} = \beta_0 + \beta_1(Sex_i) + s_1(Age_{ij}) + u_i + error_{ij}$$

here β_1 denotes the parameter estimate of sex. In the following step we tested for age varying differences between males and females by including a sex varying smooth function (age by sex interaction effect):

$$y_{ij} = \beta_0 + s_1(Age_{ij}) + s_2(Age_{ij})Sex + u_i + error_{ij}$$

here s_2 allows to test whether the smooth functions for males and females differ. These three models were compared using the Bayesian Information Criterion (BIC), the model with the smallest BIC value was selected as the best-fit model to describe developmental and sex effects of y_{ij}.

For analysis 3) and 4), models were separately assessed for males and females, given that puberty had different timing in males and females. The best developmental model was selected by examining whether PDS would be a better predictor for development than chronological age. To do so two models including smooth age and smooth PDS terms were compared:

$$y_{ij} = \beta_0 + s_1(Age_{ij}) + u_i + error_{ij}$$

$$y_{ij} = \beta_0 + s_1(PDS_{ij}) + u_i + error_{ij}$$

The best-fit developmental model was selected using BIC. For analysis 4) the best-fit developmental model was compared to a model including smooth effects of testosterone level:

$$y_{ij} = \beta_0 + s_1(Testosterone_{ij}) + u_i + error_{ij}$$

here s_1 represents the smooth term for testosterone level for each individual per time point. To account for collinearity between age and testosterone levels we additionally checked whether the effect of testosterone would still be significant when including age ($Age0$) or PDS ($PDS0$) at baseline in the model:

$$y_{ij} = \beta_0 + s_1(Testosterone_{ij}) + Age0_i + u_i + error_{ij}$$

$$y_{ij} = \beta_0 + s_1(Testosterone_{ij}) + PDS0_i + u_i + error_{ij}$$

Again the best-fit model was selected using BIC values.

In analysis 5) we aimed to test whether same aged individuals in earlier stages of puberty would show difference in brain structure compared to their peers. PDS was transformed into z scores, per age bin, full years (e.g. 8 year olds, 9 year olds). These scores were created for each individual i at each time point j. Next z-scores were divided into two groups ($zPDSgroup$)of early and later pubertal stage. Next a model including smooth effects of age only was compared to a model including both a smooth age effect and a main effect of PDS group.

$$y_{ij} = \beta_0 + \beta_1(zPDSgroup_{ij}) + s_1(Age_{ij}) + u_i + error_{ij}$$

Next interaction effect of PDS group by age was assessed with the following model.

$$y_{ij} = \beta_0 + s_1(Age_{ij}) + s_2(Age_{ij})zPDSgroup_{ij} + u_i + error_{ij}$$

In this exploratory analysis model fits including significant p-values ($p < 0.05$) are reported for β_1 and s_2.

To further disentangle the effects of testosterone on brain development we also estimated relative testosterone levels by transforming values of testosterone into z scores, in analysis 6). In this way we could identify individuals that had higher or lower levels of testosterone compared to their peers. Values were transformed into z-scores by age bin (full year; $zTestosterone_{ij}$). These scores were created for each individual i at each time point j. For this last set of analysis z-scores were divided into two groups. Such that each $zTestosterone_{ij}$ value was assigned to high or low testosterone group ($zTestosteronegroup_{ij}$).

$$y_{ij} = \beta_0 + \beta_1(zTestosteronegroup_{ij}) + s_1(Age_{ij}) + u_i + error_{ij}$$

here β_1 denotes the parameter estimate of testosterone group (high or low). In the following step we tested for age varying differences between high and low testosterone groups by including a testosterone group varying smooth function:

$$y_{ij} = \beta_0 + s_1(Age_{ij}) + s_2(Age_{ij})zTestosteronegroup_{ij} + u_i + error_{ij}$$

here s_2 allows to test whether the smooth functions differ for individuals with high and low testosterone groups.

To test whether testosterone effects are puberty specific, we separately analyzed individuals in the pubertal age range (10–18-years), where collinearity between testosterone and age is high, and individuals in the post-pubertal age range (> 18 years old).

2.3.2. Intra-class correlations

To test for homogeneity of the data in this longitudinal sample intra class correlation (ICC) was tested for $zTestosterone_{ij}$ and $zPDSgroup_{ij}$ and ROIs. ICC values were computed by estimating a null model including a random intercept for each participant dividing. Next, the variance of the intercept is divided by the sum of the variance in intercept and residual variance. ICC values are reported in Table 2.

3. Results

3.1. Relation between age, sex and puberty measures

3.1.1. Pubertal status

Age and sex effects on pubertal status as assessed with PDS scores

Table 2
ICC for all variables.

Measure	ICC
PDS	0.417
log(testosterone)	0.535
Caudate	0.93
Putamen	0.881
Pallidum	0.87
Accumbens	0.803
Cerebellum grey	0.933
Thalamus	0.938
Hippocampus	0.927
Amygdala	0.933

Table 3
Generalized additive mixed-effects models examing sex and age effects on pubertal measures and ROIs.

Measure	Model	Sex		Age spline			Age x Sex spline		
		Estimate	*p*-value	EDF	F	*p*-value	EDF	F	*p*-value
PDS	age + sex	−0.259	**	2.951	265.442	**			
Testoterone	age × sex	1.536	**	2.877	16.009	**	2.91	82.107	**
Caudate	age + sex	461.728	**	1	1.107	0.293			
Putamen	age + sex	811.784	**	2.359	26.700	**			
Pallidum	age + sex	255.264	**	2.757	13.738	**			
Accumbens	age + sex	73.473	**	1.012	38.277	**			
Cerebellar cortex	age × sex	9306.714	**	2.82	82.828	**	2.575	9.984	**
Thalamus	age + sex	870.512	**	2.869	30.285	**			
Amygdala	age + sex	286.466	**	2.326	3.234	0.101			
Hippocampus	age + sex	448.692	**	2.459	3.175	0.091			

For the age spline and the age-by-group splines, the estimated degrees of freedom (EDF), F-value, and *P*-values are reported.
** *P*-value < 0.001.

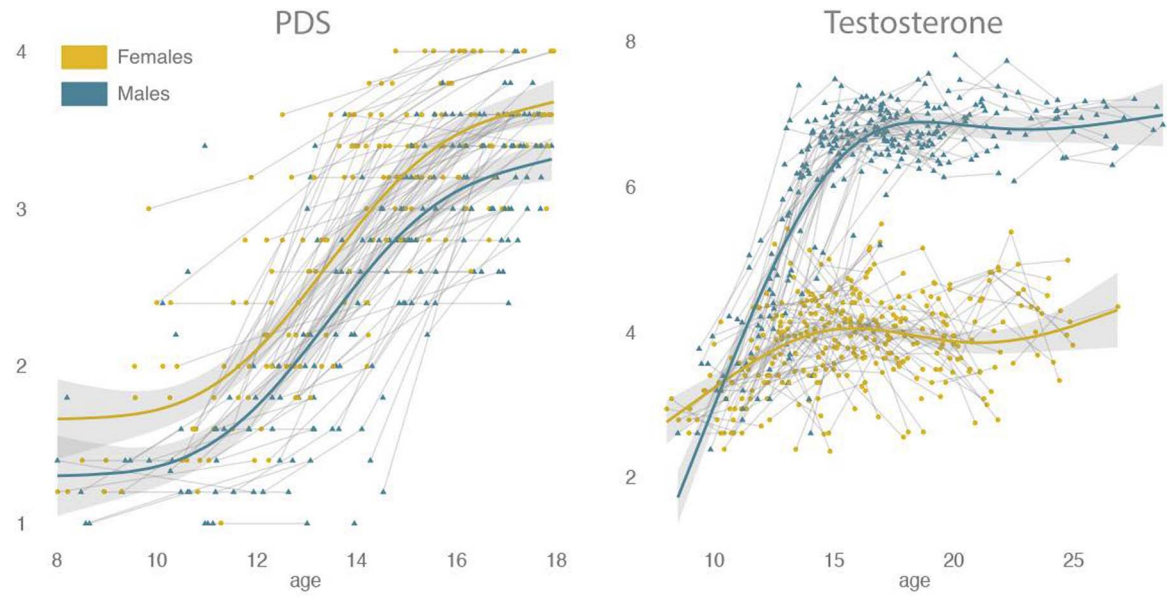

Fig. 1. Age by sex effects on PDS (Left) and log transformed Testosterone levels (Right).

were examined for the 416 available data points. The best-fit model included main effects of age and sex (see Table A1 and Table 3). The model fit can be observed in Fig. 1(Left). The fastest change in PDS was observed between 11.0 and 15.0 years in females and between age 12.2 and 16.2 in males, as estimated with the first derivative of the slopes. This confirms that females show more mature physical characteristics of puberty at an earlier age than males as assessed with the PDS scale.

3.1.2. Testosterone

Age and sex effects on testosterone were examined for the 523 available data points. The best-fit model for testosterone level included an age by sex interaction effect (see Table A1 and Table3 and Fig. 1 (Right)). Males showed rapid increases in testosterone level followed by more stable levels thereafter. In females, there was a modest increase in testosterone observed. As developmental trajectories of testosterone differed between the sexes, all follow up analyses including testosterone levels were performed separately for males and females.

3.2. Relation between chronological age, sex and ROIs

In order to test for the effects of age and sex on the ROIs, generalized additive mixed modeling was used. Best-model fits were selected using BIC values (see Table A1). All ROIs showed significantly larger volumes in males than females (see Fig. 2 and Table 3). Additionally, the putamen, pallidum, nucleus accumbens, cerebellar cortex and thalamus volumes showed age related changes as indicated by significant age spline effects (Table 3). Putamen showed a non-linear increase in volume across the age range, while pallidum showed a somewhat non-linear increase. In contrast, nucleus accumbens showed a linear decrease with age, and thalamus volumes showed a curvilinear pattern with volume decrease seen in mid-adolescence. The cerebellar cortex was the only region showing an age by sex interaction; its volume showed an early increase followed by decrease in males, while females showed a curvilinear decreasing trajectory.

3.3. Developmental models: chronological age vs puberty

We tested whether any observed age-related changes in subcortical and cerebellar brain volumes would be related to pubertal maturation. To explore potential puberty specific effects on brain structure we tested whether puberty is a better predictor of brain development than chronological age. Therefore, for each ROI we compared models including a smooth age effect to models including a smooth effect of PDS. The best-fit developmental model (age or PDS) was selected using BIC values. When PDS was the best model predictor we also tested whether these results remained significant after including baseline age, e.g. age at which participants entered the study, as a covariate in the developmental model.

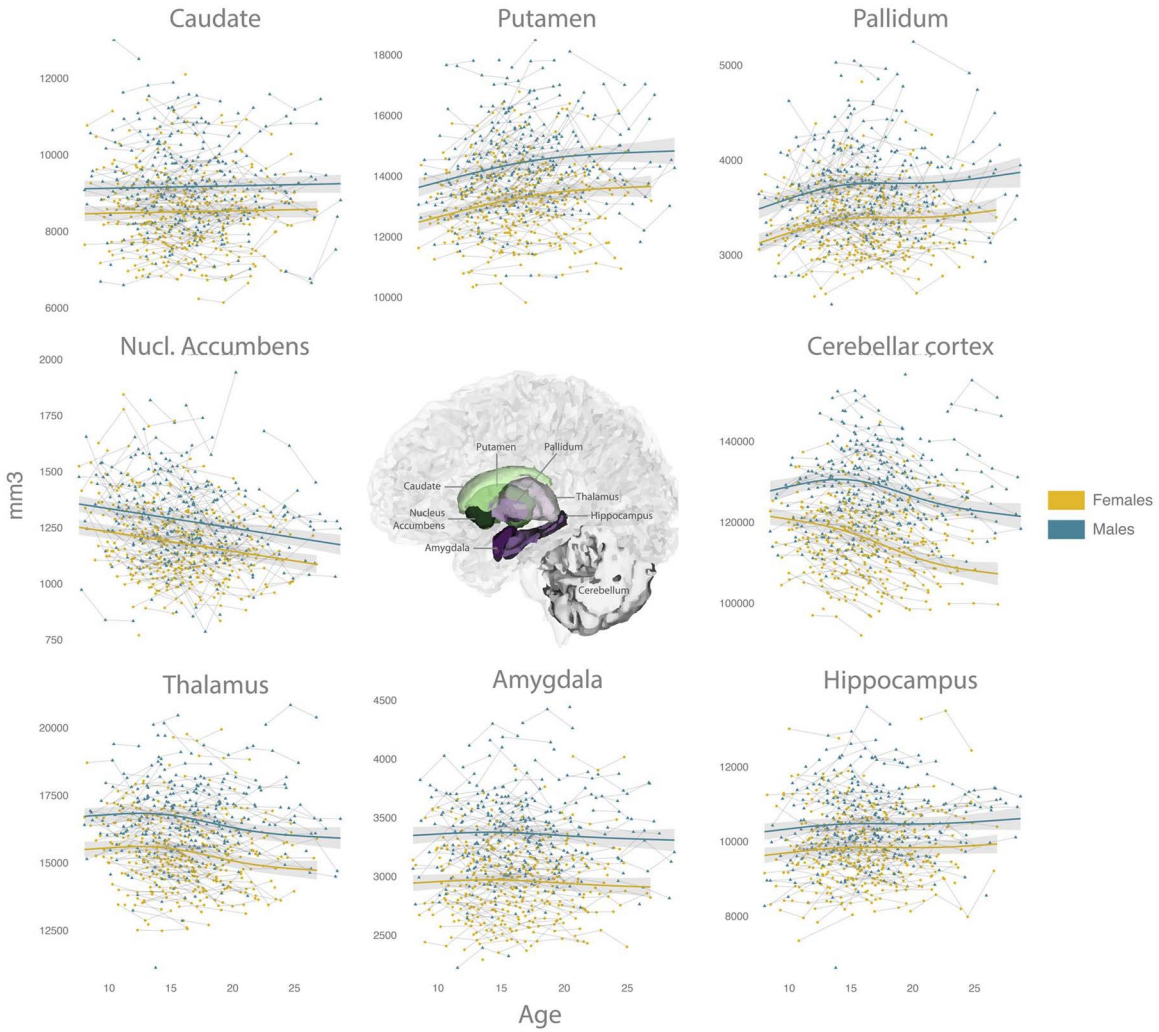

Fig. 2. Best GAMM model fits of age and sex for each brain volume. Main effects of sex were observed for all ROIs, significant age effects were observed for putamen, pallidum, nucleus accumbens, cerebellar cortex and thalamus volumes, whereas an additional sex by age interaction effect was observed for the cerebellar cortex.

Table 4
Model fits for genralized additive mixed-effect models examining the smooth effects of age, puberty and testosterone on brain volume for our ROIs.

Sex	Measure	Best model fit		Age only			PDS only				Testosterone only				
		Maturation	Testosterone	EDF	F	*p*-value	EDF	F	*p*-value		EDF	F	*p*-value		
Males	Caudate	PDS only		1	0.854	0.357	1	2.84	0.094	A	1	0.045	0.832		
	Putamen	PDS only		1	19.229	**	1	20.447	**	A	1	10.146	**	A	B
	Pallidum	PDS only	testos only	1	3.946	*	1	4.391	*	A	1	7.535	**	A	B
	Accumbens	PDS only	testos only	1	1.383	0.241	1	2.58	0.11		1	4.172	*		B
	Cerebellar cortex	PDS only		2.267	4.005	*	2.342	5.198	**	A	1	1.992	0.16		
	Thalamus	PDS only		1	11.548	**	1	22.307	**	A	1	14.975	**	A	B
	Hippocampus	age only	testos only	1.713	3.529	0.119	1	2.264	0.134		1	5.705	*	A	B
	Amygdala	PDS only	testos only	1	1.957	0.164	1	3.664	0.057		1	4.345	*	A	
Females	Caudate	PDS only	testos only	2.132	2.793	0.094	2.134	3.616	*	A	2.37	4.603	*	A	B
	Putamen	age only		2.089	11.023	**	1	12.255	**	A	1	1.103	0.295		
	Pallidum	PDS only		1	3.301	0.071	1	5.933	*	A	1.67	1.44	0.14		
	Accumbens	age only		1	8.689	**	1	6.487	*		1	2.114	0.148		
	Cerebellar cortex	age only		2.052	42.369	**	2.187	20.827	**	A	1	0.185	0.667		
	Thalamus	age only		2.508	14.427	**	1	4.736	*		1	0.748	0.388		
	Hippocampus	PDS only	testos only	1.205	0.06	0.754	2.173	2.188	0.073		1	2.503	0.115		
	Amygdala	age only		2.308	2.944	*	1.662	0.932	0.325		1	0.208	0.649		

BIC = Bayesion Information Criterium. For regions where testosterone was the best spline fit model the estimated degrees of freedom (EDF), F-value, and P-values are reported.
[A] Reflects significant p-value ($p < 0.05$) of PDS/testosterone after covarying for age at which individuals entered the study.
[B] Reflects significant p-value ($p < 0.05$) of testosterone after covarying for PDS with which individuals entered the study.
* p-value < 0.05.
** p-value < 0.01.

Model comparisons can be found in Table B1 and spline fit effects of age and PDS in Table 4. In males all ROIs, with exception of the hippocampus, where better described by PDS than by chronological age as reflected by smaller BIC values (see Table B1). Moreover, PDS showed significant effects for the putamen, pallidum, cerebellum grey and thalamus volumes, which also remained significant after including age at baseline in the model.

In females PDS was a better fit than chronological age for caudate, pallidum and hippocampal volumes, of which caudate and pallidum volumes were significantly related to PDS also after including age at baseline in the model. Putamen, nucleus accumbens, cerebellar cortex, and thalamus volumes also showed significant PDS effects, but the PDS model did not better describe the data than chronological age. Amygdala volume was the only structure that showed no significant effect of PDS in females, it did show a significant age effect.

3.4. Developmental effects of testosterone

Next, we explored whether the developmental effects observed above were related to developmental changes in testosterone level. To do so we tested whether variation in testosterone level would better explain brain volume change than chronological age or pubertal stage. To test this we compared the best-fit developmental model selected above (age or PDS) to a model including (log transformed) testosterone level. As the testosterone level in the pubertal phase is highly correlated with age we also tested whether these results remained significant after including baseline age as a covariate in the model.

Results of spline fits for testosterone level can be observed in Table 4 and BIC values of best model fits in Table B1. In males, pallidum, accumbens and amygdala volumes were better described by testosterone level than by a developmental model including PDS. These three structures showed significant effects of testosterone level, which for pallidum and amygdala also remained significant after covarying for age at baseline. Additionally, hippocampal volume was better described by testosterone level than chronological age, also after covarying for age at baseline.

In females caudate and hippocampal volumes were better described by a model including testosterone than PDS. The effect of testosterone on caudate volume was also significant after co-varying for age at baseline. Interestingly, pallidum volume showed a significant effect of PDS but not testosterone.

3.5. Puberty in age-matched peers

To test whether same aged individuals in different pubertal stages vary in brain structure we compared PDS scores using age-binned z-scores. Participants were assigned to low and high puberty groups for each time point separately. We next modeled main and interaction effects of PDS group by age to explore whether individuals with high PDS scores at earlier ages would show different structure across the age range or would show a different developmental trajectory in a given ROI. These analyses were performed separately for males and females.

Pallidum volume showed a significant interaction effect in males and a non-significant interaction effect in females, where greater volume in early adolescence was observed in individuals with early pubertal status. Caudate volume showed a significant age by PDS group interaction effect in females, where earlier maturing individuals showed larger volume than later maturing girls. These interaction effects may indicate that same aged individuals in more developed stage of PDS (early pubertal maturation) have somewhat accelerated brain developmental trajectories compared to their peers (See results in Table C1 and Fig. 3).

3.6. Puberty specific effects of testosterone

It is challenging to disentangle the effects of testosterone level and "maturation" in this age range due to the large increases in testosterone level, and consequently high collinearity between testosterone, PDS and age. Therefore, we further compared testosterone levels of same-aged individuals by estimating age-binned z-scores. Participants were assigned to low and high testosterone groups for each time point separately. We first tested whether in the pubertal age range (10–18-years) individuals with relative high levels of testosterone would show a different developmental trajectory in brain structure than individuals with relative low levels of testosterone. Secondly, we tested whether these testosterone levels would show differences in brain structure that are stable across the age range, by comparing the pubertal to the post pubertal age period. Testosterone groups were modeled across age, and *p*-values of both main testosterone group and testosterone by age interaction effects were reported to explore the effects of testosterone on brain development in individuals in the pubertal (younger than 18 years) and post-pubertal age range (18 years or older). This resulted in two groups of 232 individuals (472 scans) and 82 individuals (151 scans) respectively. These analyses were performed separately for males and females.

Results can be found in Table D1 and Fig. B1 . In pubertal males we observed different slopes for the testosterone groups in thalamus volume, such that a faster decline was observed in individuals with lower testosterone levels compared to their peers. In the post-puberty age range this effect was not significant. For the cerebellar cortex we observed a main effect of testosterone in puberty, such that larger testosterone values are associated with larger volumes. In females different developmental trajectories between testosterone groups were observed for hippocampal volume in the post-pubertal age range, with accelerated growth in girls with lower levels of testosterone compared to their peers. This was not observed in the pubertal age range.

4. Discussion

The main aim of the present study was to delineate age trajectories and disentangle these from effects of pubertal changes on subcortical brain volumes and the cerebellum. Significant age related changes were observed for most volumes for both males and females, with a heterogeneous pattern of both volume increases and decreases with increasing age. Furthermore, we used a novel approach to test pubertal effects beyond age and found that self-reported pubertal status better described development in several brain structures than chronological age. Next, we observed that puberty related increases in testosterone were associated with developmental changes in some subcortical brain volumes. These patterns allow us to hypothesize on developmental mechanisms involved in different regions; they may inform us about puberty and non-puberty specific effects, and help us unravel where in the brain testosterone may have organizing or accelerating developmental effects. We will address the specific patterns for each subcortical structure in the following section.

The basal ganglia structures showed a heterogeneous pattern of development where pubertal effects differed for males and females. More specifically, caudate volume showed no significant age related change across the full age range. However, there was a puberty specific effect where individual differences in PDS better described change in this structure than chronological age. This effect was significant in females, where a peak in caudate volume was observed at intermediate levels of self-report puberty measures. This female specific finding replicates results of Goddings et al. (2014), but is not in line with a cross-sectional study that reported no pubertal effects on caudate volume (Bramen et al., 2011). Our data indicate that in females pubertal changes in the caudate might be sensitive to fast changes in testosterone. We additionally observed that females in earlier phases of puberty showed an earlier peak in caudate volume compared to peers. This supports the notion that puberty, in particular testosterone, may be the driving source behind previously observed inverted-U shaped trajectory in this structure (Tamnes et al., 2013; Lenroot et al., 2007;

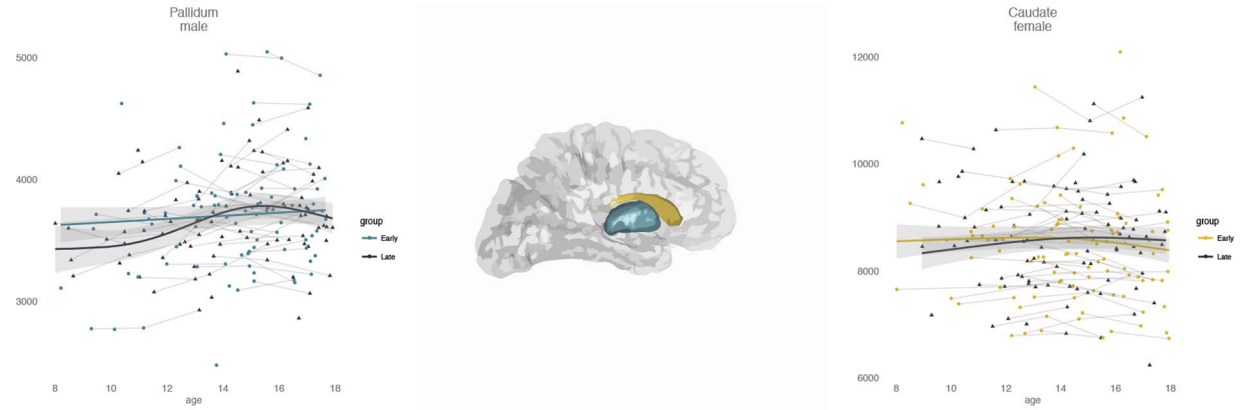

Fig. 3. Different trajectories for individuals in earlier compared to late stages of puberty compared to peers. In males (left) for pallidum volume and females (right) in caudate volume.

Wierenga et al., 2014). These results are in line with findings of Herting et al. (2015), who showed an interaction effect of age by puberty (Tanner stage and testosterone). The observed stable volumes in older adolescents, suggest that puberty may have an accelerating effect on brain changes in caudate volume.

A second region that is part of the basal ganglia, the putamen, also showed significant associations with change in PDS. Specifically, the putamen showed an age related increase in puberty, leveling off in late adolescence. In line with findings of Goddings et al. (2014) this volumetric increase was significantly associated with secondary sexual characteristics in males. These results suggest that in males PDS might be associated with developmental changes in this structure, while in females they merely coincide. Interestingly, this was not observed for testosterone. Possibly, puberty related processes other than testosterone drive changes in this brain region. Biro et al. (2014) showed that in females development of secondary sexual characteristics are preceded by increases in DHEA and estradiol. Increases in testosterone prior to onset of secondary pubertal characteristics were relatively late. This could explain dissociable effects of PDS and testosterone on putamen development.

Pallidum volume also showed a puberty specific effect. First and in line with previous findings, a curvilinear change with age was observed, with fast changes in puberty followed by a more stable period in late adolescence (Wierenga et al., 2014; Tamnes et al., 2013). For both sexes, PDS was the foremost predictor of change in this region, confirming previous results (Goddings et al., 2014). In males, this developmental pattern was related to changes in testosterone level. Moreover, males that showed later onset of puberty compared to their age-matched peers had smaller volumes pre-puberty and accelerated growth in puberty. The puberty related increases in volume suggest that marked changes take place in this period, possibly indicative of reorganizational processes. Additionally, in males these reorganizing effects may be driven by changing levels of testosterone. In girls however, PDS but not testosterone was the best fit model, as such other hormones as described above could be related to changes in this structure (Biro et al., 2014).

For the final region of the basal ganglia, the nucleus accumbens, we did not find an association with PDS, which contrasts findings of Goddings et al. (2014). In line with previous findings on age trajectories, we did observe decreasing volumetric changes with age in both males and females (Ostby et al., 2009; Tamnes et al., 2013; Wierenga et al., 2014; Goddings et al., 2014). In males, volumetric changes in puberty were significantly related to testosterone. Interestingly, functional imaging studies showed that activity in this region peaked in mid-adolescence (Braams et al., 2015), which coincides with the rapid structural decreases observed in our study.

Similar to regions in the basal ganglia, sex specific effects of puberty were also observed for the thalamus. As expected, its volume showed a curvilinear trajectory, peaking in early puberty and decreasing thereafter (Tamnes et al., 2013, Wierenga et al., 2014). In males, volume decreases were associated with change in PDS, and change in testosterone. No such effect was observed in females suggesting that these effects may be gender specific. In addition, males that showed higher pubertal related testosterone levels (i.e. earlier rises in testosterone level) than their peers had more precipitous change in volume. This finding suggests that the onset of testosterone increase has an accelerating effect on the typical development of this trajectory. This sexual dimorphic effect may explain why previous studies did not observe pubertal effects on thalamus volume (Bramen et al., 2011; Herting et al., 2015). This implies that these effects should be modeled separately for the sexes.

Hippocampal and amygdala structures showed a different pattern than basal ganglia and thalamus structures, where testosterone effects were not restricted to the pubertal age range. First, volumes of the amygdala and hippocampus did not show significant maturational changes across the full age range. This is in line with the previously described pattern that medial temporal lobe structures appear to follow different developmental trajectories across adolescence than most of the other subcortical structures, with less pronounced changes (Mills and Tamnes, 2014). However, in the pubertal age range, these volumes were predicted by changing levels of testosterone, where larger testosterone levels were associated with larger volumes, albeit this did not reach significance in females. The observation that PDS was not significant in this structure supports that these effects are testosterone specific. We did observe that females in the post-pubertal age range with relative high levels of testosterone show decelerated volume changes in the hippocampus. This sexual dimorphic effect of testosterone on hippocampal development is in line with earlier work (Bramen et al., 2011; Satterthwaite et al., 2014), however this was not observed in other studies (Neufang et al., 2009; Hu et al., 2013; Goddings et al., 2014; Herting et al., 2015). Non-human primate studies indicated that the hippocampus is highly sensitive to sex steroids as it has a relatively high number of estrogen receptors (Morse et al., 1986). As such, sex differences in levels of gonadal hormones may have particular strong sexual dimorphic effects on this structure. Also, the amygdala is highly sensitive to sex steroids as a relative large number of androgen receptors is observed (Clark et al., 1988), which is in line with our observation that males but not females show pubertal effects for this structure. In addition, rodent studies observed that increases in the number of astrocytes in amygdala subparts are driving the sex difference in cell number and volume of this structure (De Lorme et al., 2012). Our findings suggest prolonged effects of testosterone on hippocampus and amygdala volumes that are not specific to puberty or sex. This is in line with findings in animal studies that showed that for some brain structures perinatal and pubertal periods do not represent two distinct sensitive periods, also in childhood hormone exposure may

have organizing effects. It is hypothesized that for these structures puberty may represent a sensitive window as a function of heightened levels of pubertal hormones (Schulz and Sisk, 2016).

In contrast to the subcortical structures, the cerebellar cortex showed sexual dimorphic developmental trajectories across the age range, confirming scarce number of previous studies (Tiemeier et al., 2010; Wierenga et al., 2014). For both males and females significant associations with PDS were observed, however for females this model did not exceed the age model, suggesting a general developmental pattern. Testosterone changes in puberty were not associated with changes in the cerebellum. However, the timing of puberty related testosterone change did show an association with volume of the cerebellum, where males that showed earlier rises in testosterone had larger volumes than their peers. Given that differences in volume were present before the onset of puberty, may suggest that the large cerebellar volume and early rises in testosterone are influenced by common genetic mechanisms. Some evidence to support this possibility comes from a voxel based morphometry (VBM) study that observed larger total cerebellar volume in women without a normal second X chromosome (Cutter et al., 2006). Furthermore, it was found that larger gray matter volume of the cerebellar hemispheres could explain the larger total cerebellar volume (Cutter et al., 2006). In addition to a genetic driven sexual dimorphism in cerebellar morphology, organizational effects of endogenous steroid hormones levels also plays a role on cerebellar volumes. For example, androgen receptors located on Purkinje cells of the cerebellar cortex are target points for endogenous testosterone modulation in the male rate brain (Perez-Pouchoulen et al., 2016). The presence of androgen receptors in the cerebellum could, at least in part, explain the positive correlation between testosterone levels and cerebellar gray matter volumes in male healthy volunteers (Schutter et al., 2017). Taken together, the results suggest that both genetic and organizational effects of steroid hormones play a role in cerebellar development and morphology.

This study has several strengths, including a large sample, longitudinal assessments, assessing both self-report pubertal stage and testosterone. This allowed us to use model selection procedures to disentangle age and pubertal effects. However, the study also had some limitations, which should be noted. First, the self-report nature of the PDS score might be biased by under and over estimations depending on the participants age (Shirtcliff et al., 2009). Second, several of the investigated brain structures are known to be cytoarchitectonically and functionally heterogeneous, and from animal studies it is indicated that sub-regions within the amygdala show divergent developmental changes when exposed to hormones (Schulz et al., 2009). Hence, future studies would benefit from studying sub-regions in these brain structures.

In sum, our results are largely in line with earlier cross-sectional and longitudinal studies. Note that we extended previously used modeling procedures by aiming to delineate age and pubertal effects. As such, discrepancies between our findings and previous work could be related to our study design in combination with the modeling procedure. As such, the results in the present paper support the notion that development of subcortical brain structures is related to inter-individual differences in pubertal change even when there were no significant effects of age or puberty specific sex dimorphic trajectories. Although speculative, the puberty specific testosterone effects are in line with non-human literature that this developmental phase marks a sensitive period where changes in hormone levels may have reorganizing effects on human brain development. As such, puberty related hormone increases may play a crucial role in the development of these structures. For example, affective disorders and symptoms also typically emerge at the end of puberty and these problems often remain into adulthood. It might be that the steroid-induced puberty reorganizing effects on the human brain, specifically in regions related to emotion expression, may trigger the rise of symptoms in this unique time-window (Paus et al., 2008). Note that there is little support for complete dichotomic structure or differential developmental patterns as we observed that even in the presence of main sex differences there is large overlap between male and female brain volumes and mostly parallel developmental trajectories. Despite the lack of dichotomous structures or trajectories we showed that the interactions between puberty-related developmental processes and subcortical brain structure differ between the sexes, which suggests that sex differences in the brain take place at the level of underlying neurochemical and molecular mechanisms that are not detectable when solely comparing sex differences on the level of brain volumes.

Conflicts of interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/ 10.1016/j.psyneuen.2018.02.034

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