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Sex effects on structural maturation of the limbic system and outcomes on emotional regulation during adolescence

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ABSTRACT

Though adolescence is a time of emerging sex differences in emotions, sex-related differences in the anatomy of the maturing brain has been under-explored over this period. The aim of this study was to investigate whether puberty and sexual differentiation in brain maturation could explain emotional differences between girls and boys during adolescence. We adapted a dedicated longitudinal pipeline to process structural and diffusion images from 335 typically developing adolescents between 14 and 16 years. We used voxel-based and Regions of Interest approaches to explore sex and puberty effects on brain and behavioral changes during adolescence. Sexual differences in brain maturation were characterized by amygdala and hippocampal volume increase in boys and decrease in girls. These changes were mediating the sexual differences in positive emotional regulation as illustrated by positive attributes increase in boys and decrease in girls. Moreover, the differential maturation rates between the limbic system and the prefrontal cortex highlighted the delayed maturation in boys compared to girls. This is the first study to show the sex effects on the differential cortico/subcortical maturation rates and the

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interaction between sex and puberty in the limbic system maturation related to positive attributes, reported as being protective from emotional disorders.

1. Introduction

Adolescence is a sensitive period of gradual transition from childhood to adulthood (Spear, 2000) through maturation of adult social and cognitive behaviors (Sisk and Foster, 2004). Adolescence is characterized by important pubertal changes and the passage from immature child brain to adult brain through complex maturational processes such as synaptic pruning, dendritic and axonal arborization, and myelination (Lenroot and Giedd, 2006). It is also a period of emerging sex differences such as on brain and behaviors. Hormonal changes related to puberty are partly responsible for the development of the brain (Spear, 2000) and of the cognitive functions (Blakemore et al., 2010). Onset of pubertal maturation occurs in the brain with some neural changes leading to hormone levels increase themselves responsible for other brain changes (Dahl, 2004). The pubertal timing being different between boys and girls, age alone is unfit for looking at sex-related maturation differences during adolescence. Thus, reliance on pubertal landmarks rather than age appears more adapted for studying sex and maturation processes during adolescence.

Sex effects on brain macrostructural maturation as studied with Magnetic Resonance Imaging (MRI) has been described as a global grey matter (GM) volume peak reached earlier in girls followed by a steeper GM volume decrease rate compared to boys on a classical inverted U-shape maturation curve (Aubert-Broche et al., 2013; Herting and Sowell, 2017; Raznahan et al., 2014). Furthermore, global white matter (WM) volume follows a steeper linear WM volume increase in boys as compared to girls. Additionally, the sexual differences of white matter microstructure investigated with Diffusion Tensor Imaging (DTI) draw less consistent findings (Tamnes et al., 2018). Some studies reported sex differences in WM microstructure maturation (Herting et al., 2012; Schmithorst et al., 2008; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012) while others studies have reported few or no significant sex-by-age interaction (Bava et al., 2010; Eluvathingal et al., 2007; Giorgio et al., 2010). Regional patterns of sexual differences in macrostructural maturation trajectories have also been reported, notably in the limbic system with the amygdala, the hippocampus and the prefrontal cortex where girls showed an early maturational peak as compared to boys (Eliot, 2019; Goddings et al., 2014; Herting et al., 2018; Lenroot et al., 2007). However, other studies did not find sex by age interaction during adolescence for subcortical regions such as basal ganglia, thalamus, hippocampus or amygdala (Koolschijn and Crone, 2013; Wierenga et al., 2018).

Affective disorders are also part of the pattern of sexual differences with approximately 2:1 female:male prevalence ratio during adolescence (Angold et al., 1999, 1998; Angold and Costello, 2006). Previously cited limbic regions had been implicated in the so-called “developmental mismatch hypothesis” proposing that the subcortical structures maturing earlier than the cortical structures was leading to the stereotypical adolescent behavior (see review by Mills et al., 2014). Simmonds et al. (2014) found that frontosubcortical WM connections (uncinate fasciculus, superior longitudinal fasciculus and cingulum) implicated in emotional processing mature later than most white matter bundles during childhood. Further, another study found that depressed patients had lower fractional anisotropy in this cortical-subcortical connectivity (Versace et al., 2010). In the case of the limbic system, the maturational mismatch could be related to the increase emotional reactivity and sensitivity, and thereby to an increase risk for affective disorders during adolescence compared to childhood (Casey et al., 2008).

Research on emotion dysregulation during adolescence has given a large prominence to the emotional symptomatology (i.e. depression, bipolar disorder, and anxiety disorder) but less to positive attributes (e.g. generosity, reliability, good sense of humor) that are related to the adolescent’s well-being (Gillham et al., 2011) and may be protective from emotional disorders (Vidal-Ribas et al., 2015). Once again, pubertal timing plays an important role in the emotional dysregulation with increased risks when girls mature too early or when boys mature too late (Graber, 2013).

In the literature, most of the results on sex differences in brain maturation during adolescence were based on cross-sectional study designs with large samples or large age ranges (Koolschijn and Crone, 2013; Menzies et al., 2015; Satterthwaite et al., 2014). Although informative, cross-sectional studies are limited because they can only provide estimated and not individual trajectories. The existing longitudinal studies neither included a large sample size (Bava et al., 2010; Giorgio et al., 2010; Dennison et al., 2013) nor had a large age range, nor focused on sexual differences because of the non sex parity of their sample (Bava et al., 2010; Dennison et al., 2013; Giorgio et al., 2010; Lebel and Beaulieu, 2011; Wierenga et al., 2014). Recently, few longitudinal studies had the power to tackle the question of sex differences in brain maturation during adolescence (Fish et al., 2019; Wierenga et al., 2018) but more are needed to disentangle the effect of sex, age and puberty.

For these reasons, this study investigated the sex and puberty effects on brain and behavioral changes during adolescence by – 1. taking advantage of a two time point longitudinal design of a large sample of adolescents with the same age at 14 and 16 years old and a dedicated longitudinal preprocessing methodology (Ashburner and Ridgway, 2013) – 2. looking at the sexual differences of the brain maturation with a multimodal neuroimaging approach focusing on grey and white matter using whole brain and specific limbic system regions of interest analyses - 3. linking during puberty the sexual maturation differences of the limbic system to the emotional dysregulation using psychopathological measures related to affective disorders and also personality traits that may constitute vulnerability factors. We hypothesized that boys and girls would have a different developmental mismatch in grey matter regions and white matter bundles of the limbic system, and that this differential maturation would be in return related to sex differences on emotion regulation and psychopathology during adolescence.

2. Materials and methods

2.1. Participants

Longitudinal datasets from three hundred and thirty-five adolescents (175 females; 160 males) were drawn from the Imagen database, a larger sample recruited in eight European cities at the age of 14. Two sites (138 and 197 subjects from Paris and Dresden respectively) conducted an MRI exam at both 14 and 16 years old in addition to questionnaires and neuropsychological battery tests at both times. Written informed consent and assent had been given by both parents and participants. The study had been approved by the local ethic committees. A detailed description of recruitment and assessment procedures, and exclusion and inclusion criteria has been published (Schumann et al., 2010). Notably, any obvious psychopathology (e.g. bipolar disorder, schizophrenia, or major neuro-developmental disorders) constituted non-inclusion criteria.

2.2. Self-report questionnaires

The pubertal measure was assessed with the Puberty Development Scale (PDS, Petersen et al., 1988), a measure of physical development with separate items for males and females. Questionnaires are adapted for each sex, such as menarche in females and voice changes in males. Substance use was reported using the Alcohol Use Disorders

Identification Test (AUDIT).

The adolescent psychiatric symptoms and their psychosocial impact were assessed with the Development and Well-Being Assessment (DAWBA, www.dawba.com), a self-administered diagnostic questionnaire consisting of open and closed questions (Goodman et al., 2000). The DAWBA generates probabilities of having DSM-IV diagnoses that are subsequently validated by experienced clinicians from the IMAGEN consortium. Diagnoses from affective disorders (e.g. anxiety, depression bands) were tested here.

Specifically, The Youth Strengths Inventory (YSI), within the DAWBA, asks about adolescent's positive attributes. The first part of the questionnaire is dedicated to "positive characteristics" (e.g. how generous, affectionate, caring he is) with 8 items. The second part of the questionnaire requests about "positive actions" that please others or things that the adolescent is proud of in 11 items (e.g. how good at sport, well behaved, polite he is proud of). Each item is scored on a three-point Likert scale (0: no, 1: a little, 2: a lot). Summing the score of each item per part generates two variables, "positive characteristics" (from 0 to 16) and "positive actions" (from 0 to 22). The sum of these two variables generates the global variable "total positive attributes" (from 0 to 38).

The Strengths and Difficulties Questionnaire (SDQ), a self-reported questionnaire (Goodman et al., 2003) generates a total difficulties score (reflecting emotional problems, conduct problems, hyperactivity and peer problems). Internalizing (i.e., anxious and depressive) and externalizing (i.e., aggressive and hyperactive) behaviors (Achenbach, 1992) can be measured with the SDQ. Externalizing score is obtained by summing conduct problems score and hyperactivity score; internalizing score is obtained by summing emotional problems score and peer problems score, each scale being ranged from 0 to 20.

2.3. Imaging acquisitions

All subjects underwent imaging exams on a SIEMENS Trio 3T scanner, including an anatomical and a diffusion sequences. All exams were assessed by a clinical neuroradiologist for structural abnormalities.

T1-weighted imaging. High-resolution T1-weighted images were collected using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence [Paris: repetition time (TR) = 2300 ms, echo time (TE) = 2.93 ms, inversion time (TI) = 900 ms, voxel size = 1.1 × 1.1 × 1.1 mm, flip angle = 9°; matrix size = 256 × 256 × 160 mm; Dresdren: TR = 1900 ms, TE = 2.26 ms, TI = 900 ms, voxel size = 1.0 × 1.0 × 1.0 mm, flip angle = 9°; matrix size = 256 × 256 × 176 mm].

Diffusion Tensor imaging. The diffusion tensor images (DTI) were acquired using an Echo Planar imaging sequence (4 b-value = 0 s/mm^2 and 32 diffusion encoding directions with b-value = 1300 s/mm^2; 60 oblique-axial slices (angulated parallel to the AC/PC line); echo time ≈ 104 ms; 128 × 128 matrix; field of view 307 × 307 mm; voxel size 2.4 × 2.4 × 2.4 mm).

2.4. Image processing

T1-weighted images. To correct for differences of neck rotation between each subject's acquisitions, all images were roughly realigned and cropped bellow the cerebellum. Then, intra-subject registration was performed using SPM12's Longitudinal Registration Toolbox (Ashburner and Ridgway, 2013) involving combining rigid-body registration, intensity inhomogeneity correction, and non-linear diffeomorphic registration. This step generates the subject's mid-point image between 14 and 16 years, the maps of the Jacobian determinants and the deformation fields estimated from each time-point scan to the mid-point image. The subject's mid-point image was segmented into grey and white matter with SPM12's Segmentation Toolbox with tissue priors simulated at 15 years using TOM8 toolbox (http://www.neuro.uni-jena.de/software/tom/). Grey and white matter maps of the mid-point image were modulated by the Jacobian determinants of each time-point. All grey and white matter maps of the mid-point images were spatially normalized to the standard space of the Montreal Neurological institute (MNI) using the DARTEL nonlinear image registration procedure. This step involves the iterative creation of their representative template and the extraction of the deformation fields from each image to the aforementioned template. The deformation fields obtained were then applied to the modulated grey and white matter maps preserving the regional amount of signal. Finally, modulated normalized maps of grey and white matters were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel. Global GM, WM and cerebrospinal fluid (CSF) volumes were computed for each participant. Total intracranial volume (TIV) was defined by summing GM, WM and CSF volumes. GM volumes were extracted from the amygdala, the hippocampus and the prefrontal cortex such as defined by Mills et al. (Mills et al., 2014) using WFU PickAtlas (SPM toolbox; http://fmri.wfubmc.edu/software/PickAtlas). The prefrontal cortex was defined by combining the following subdivisions: precentral gyrus, superior frontal gyrus (dorsolateral, orbital, medial and medial orbital parts), middle frontal gyrus (middle and orbital parts), inferior frontal gyrus (opercular, triangular, orbital parts), Rolandic operculum, olfactory cortex and paracentral lobule.

DTI. Diffusion data preprocessing was performed using FMRIB Diffusion Toolbox (FDT) in FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl) and consisted of affine registration to the first b = 0 image for head motion and eddy currents correction, brain extraction using the Brain Extraction Tool (BET), and voxel-wise diffusion tensor fitting to obtain images of fractional anisotropy (FA), mean diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD). FA maps were coregistered to the corresponding native white matter maps derived from the T1-weighted image preprocessing. Then, the coregistered images were normalized into the standard space by applying successively the intra-subject (longitudinal) and inter-subject (DARTEL) registrations done during T1-weighted image preprocessing. Additional processing was performed using FSL's Tract-Based Spatial Statistics (TBSS) toolbox (Smith et al., 2006). Normalized FA maps were eroded and mean FA image created and thinned to obtain a mean FA skeleton, which represents the centers of all tracts common to all subject. This skeleton was then thresholded to FA>0.2 to keep only the main tracts. Each subject's FA, MD, AD and RD data were then projected onto the skeleton and the resulting data fed into voxel-wise statistics. Global FA, MD, AD and RD values have been extracted for each participant. FA, MD, AD and RD were extracted from the cingulum and uncinate using the Johns Hopkins University (JHU) tractography atlas from FSL.

2.5. Statistics

Participants with bad image quality or failed processing of T1-weigthed or diffusion images, as well as participants with invalid PDS (e.g. PDS decreasing between 14 and 16) or with any symptom of alcohol misuse (AUDIT score > 6 for girls; AUDIT score > 7 for boys) were excluded (See Supplementary Fig. 1). Consequently, our final sample was constituted of 156 subjects (84 girls).

Voxel-Based Analyses. Macrostructural whole-brain voxel wise analyses were carried out within the general linear model (GLM) framework using SPM12. Subject, center, TIV, sex, PDS and sex-by-PDS interaction were included in a flexible factorial design. Analyses were performed on 312 GM and WM images (i.e. 156 subjects) with an explicit mask thresholded at 0.2. At the voxel level, statistical significance was set at $p < 0.05$ FWE (Family Wise Error) corrected for multiple comparisons. Microstructural whole-brain voxel wise comparisons on FA and MD maps were tested within a similar GLM framework using a randomization-based method within FSL (5000 permutations) in the same sample as macrostructural analyses. AD and RD were compared when differences in FA values were observed. Subject, center, sex, PDS and sex-by-PDS interaction were included in the design. Statistical thresholds were set at $p < 0.05$ FWE corrected and Threshold-Free Cluster Enhancement (TFCE) corrected. Similar voxel-based analyses of macro- and microstructures were conducted with age instead of PDS in the design.

Cluster sizes were set at least to 50 voxels. Brain locations were reported as x, y and z coordinates in Montreal Neurological Institute (MNI) space.

Other Analyses. Extracted imaging values (global and regional grey and white matter volumes, and mean values of each DTI index: FA, MD, AD and RD) and behavioral data (DAWBA, SDQ, YSI variables) were analyzed using R Cran software (version 3.3.1 "Bug in Your Hair" (2016.06.21)). Sex-by-PDS related changes on longitudinal imaging and behavioral data were analyzed using linear mixed models with restricted maximum likelihood (REML), to account for the repeated measures on each individual (lme4 package, version 1.1–12). PDS at baseline, PDS difference, sex, and sex-by-PDS difference interaction were entered as fixed effects and subject and center as nested random effects. TIV was entered as confounding variable in macrostructural analyses. Similar analyses were conducted with age instead of PDS in the statistical models. In order to assess the benefit of using PDS instead of age, we compared models with age only and models with age and PDS. We used Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), that are standardized model-fit metrics, to compare the two models and tested the favored model with the lower AIC and BIC values using a log likelihood ratio test.

Causal mediation analyses were conducted to determine whether the sex effects on longitudinal changes in macro- and micro-structures within the ROI previously identified could mediate the sex effects on longitudinal behavioral changes along puberty between 14 and 16. As prerequisite, mediation analyses were conducted only on behavioral questionnaires and ROI that have a significant sex-by-PDS interaction. The analyses were performed using a set of GLM to derive the mediation and direct effects from the total effect (mediation package, version 4.4.5). Behavioral changes (time 2 – time 1) were entered as a dependent variable, and PDS difference (time 2 – time 1), sex, PDS difference-by-sex interaction and PDS at 14 as independent variables within a regression model. Each ROI indices (time 2 – time 1) was entered as a mediator variable, sex as the treatment of the mediation, and center as confounding variable. This mediation model was performed using 5000 Monte Carlo draws for nonparametric bootstrap. In causal mediation analysis, a significant mediating effect is defined as a 95% confidence interval that does not include 0.

3. Results

3.1. PDS, sex and self-report questionnaires

Within our sample of 156 subjects (84 girls and 72 boys) analyzed at both assessment times, girls had higher PDS scores than boys but not significant difference in age (see Table 1 and Supplementary Fig. 2).

The YSI questionnaire yielded sex-by-PDS interaction with total positive attributes ($p = 0.04$, see Table 2) and more specifically on the subscale "positive characteristics" ($p = 0.02$). "Positive characteristics" and "total positive attributes" increased in boys and decreased in girls with puberty between 14 and 16 years.

No sex-by-PDS interaction was found in the SDQ or the DAWBA questionnaires (see Supplementary Table 1).

Using age instead of PDS, no significant sex-by-age interactions were found for all behavioral questionnaires but for the "positive characteristics" ($p = 0.03$, see Supplementary Table 2). We did not find a favored model comparing "age" and "age plus PDS" models (See Supplementary Table 3).

3.2. Imaging

3.2.1. Global measures

Global GM volume decreased along puberty, with a steeper rate in girls compared to boys (see Fig. 1, Table 3). Global WM volume increased with a steeper rate in boys compared to girls. Global FA increase and global MD decrease were found for all subjects but no sex-by-PDS interaction. Global GM and WM volumes followed similar changes when using age instead of PDS (see Supplementary Table 4). Global diffusion indices displayed significant sex-by-age interactions when using age instead of PDS. We did find favored models using "age plus PDS" instead of "age" only for global GM and WM volumes (See Supplementary Table 5).

Table 1
Sample demographics.

	time-point	Girls (N = 84)	Boys (N = 72)	Total (N = 156)	p-value
Non-European descents (N)	Baseline	5	6	11	0.79
Parent's Education Level (Mean ± sd)	Baseline	4.21 ± 1.52	4.06 ± 1.54	4.14 ± 1.53	0.56
Pubertal Development Scale (Mean ± sd)	Baseline	3.15 ± 0.47	2.55 ± 0.55	2.87 ± 0.59	$2.62e^{-11}$
	Follow-up	3.70 ± 0.25	3.20 ± 0.40	3.47 ± 0.41	$2.23 e^{-15}$
Age in years (Mean ± sd)	Baseline	14.43 ± 0.42	14.36 ± 0.41	14.40 ± 0.42	0.32
	Follow-up	16.70 ± 0.48	16.59 ± 0.53	16.65 ± 0.50	0.15

Notes: p values from *t*-test or X^2 tests.

Table 2
Effect of PDS by sex on psychometric measures.

task	measure	sex	score change (per PDS point)	*t*-test (degree of freedom)	p-value	interaction sex-by-PDS p-value
YSI	Positive characteristics	boys	1.06	t(1.48) = 1.32	0.35	0.02
		girls	−0.50	t(1.42) = 0.62	0.62	
	Positive actions	boys	0.08	t(8.23) = 0.13	0.89	0.34
		girls	−0.71	t(6.49) = 1.11	0.30	
	Total positive attributes	boys	1.18	t(6.51) = 1.28	0.24	0.04
		girls	−1.22	t(5.26) = 1.38	0.22	

Notes: YSI: Youth Strengths Inventory; PDS: Puberty Developmental Scale.

3.2.2. Voxel-based and regional measures

The voxel-wise sex-by-PDS interaction showed a significant steeper GM volume decrease in girls in the prefrontal cortex, caudate, putamen, thalamus, Heschl's gyrus and post-central gyrus, while boys had a significant steeper GM volume increase in the amygdala-hippocampal complex, precentral gyrus and parts of the occipital pole (see Fig. 2, Supplementary Table 6). A steeper WM volume increase was detected in boys compared to girls in most parts of the brain except in bilateral external capsule, where the volume decreased more in girls than in boys. No voxel-wise sex-by-PDS interaction was found in FA or MD. The voxel-wise sex-by-age interaction showed similar results in GM and WM volumes than the ones with PDS (see Supplementary Fig. 3 and Supplementary Table 7). Unlike the PDS, we found significant voxel-wise sex-by-age interaction for FA and MD (see Supplementary Fig. 4 and Supplementary Table 8).

ROI investigations of macrostructure confirmed sex-by-PDS interactions in amygdala, hippocampus and the prefrontal cortex, and concerning microstructure, we found only trends for a sex-by-PDS interaction in the cingulum and the uncinate but with no significant change in boys or girls taken separately (see Table 4). Boys displayed amygdala and hippocampus volumes increases and a prefrontal cortex volume low decrease whereas girls displayed amygdala and hippocampus volumes decreases and a prefrontal cortex volume low decrease. ROI investigations of macro- and microstructure showed the same sex-by-age interactions (see Supplementary Table 9).

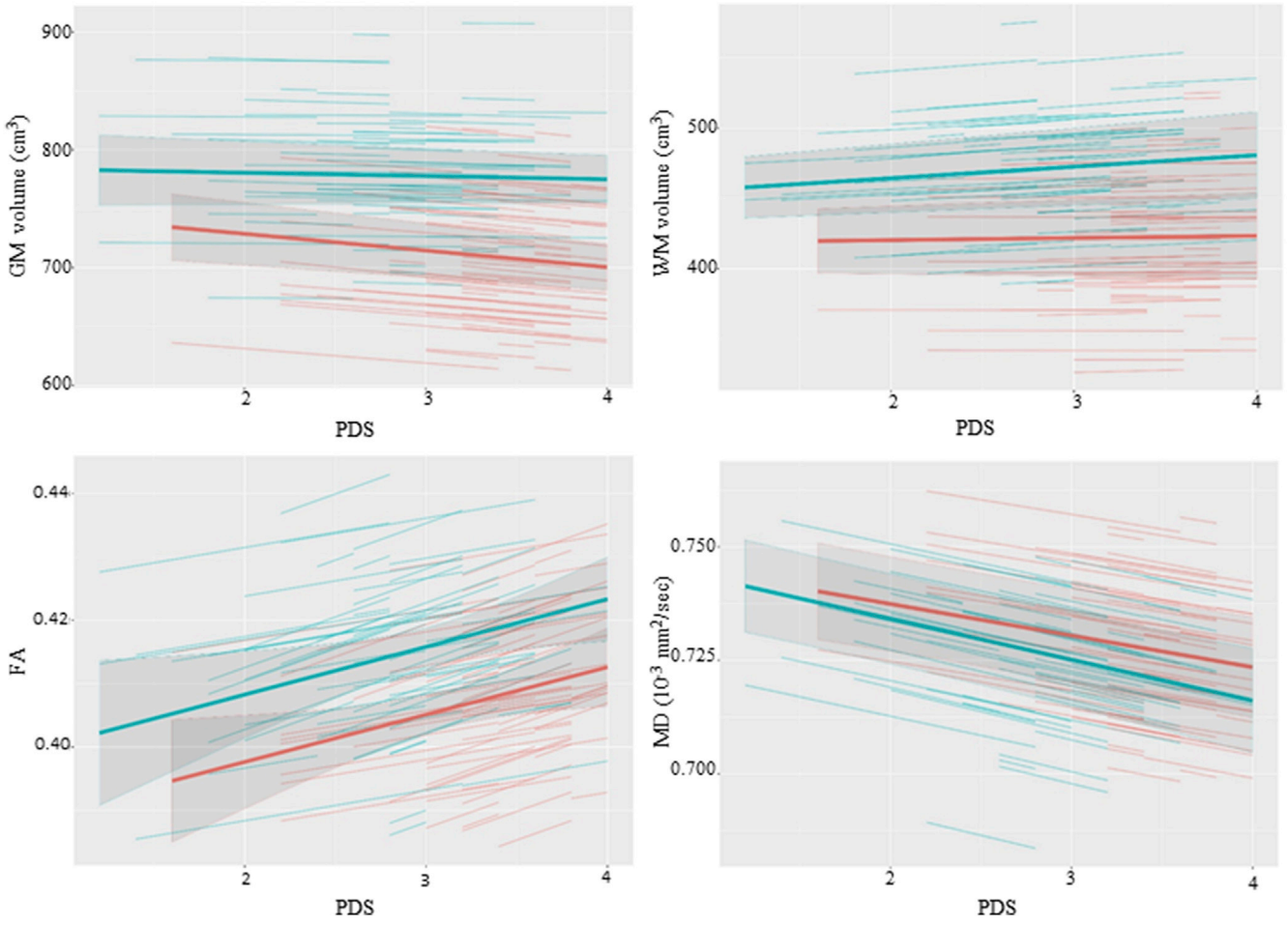

Fig. 1. Longitudinal effect of PDS on global GM and WM volumes, and global FA and MD indices. Girls are in red and boys in blue; thin lines represent individual scores; thick lines represent the linear mixed-effects model estimates. Sex-by-PDS interaction is only significant for GM ($p = 3.77\ e^{-11}$; boys: b = -2.52, t(1.30) = 1.13, p = 0.42; girls: b = −14.34, t(1.35) = 6.40, p = 0.05) and WM volumes ($p = 5.68\ e^{-16}$; boys: b = 8.24, t(1.07) = 4.55, p = 0.12; girls: b = 1.48, t(1.01) = 0.79, p = 0.57); PDS: Puberty Developmental Scale; GM: Grey Matter; WM: White Matter; FA: Fractional Anisotropy; MD: Mean Diffusivity.

Table 3
Effect of PDS by sex on global imaging measures.

imaging	global measure	sex	change estimate (per PDS point)	*t*-test (degree of freedom)	p-value	interaction sex-by-PDS p-value
T1-weighted	GM (cm^3)	boys	−2.52	t(1.30) = 1.13	0.42	$3.77e^{-11}$
		girls	−14.34	t(1.35) = 6.40	0.05	
	WM (cm^3)	boys	8.24	t(1.07) = 4.55	0.12	$5.68e^{-16}$
		girls	1.48	t(1.01) = 0.79	0.57	
DTI	FA	boys	0.0084^3	t(1.12) = 2.54	0.21	0.83
		girls	0.00814	t(1.15) = 2.42	0.22	
	MD (10^{-3} mm^2/s)	boys	$-1.02e^{-05}$	t(23.64) = 7.11	$2.56e^{-07}$	0.15
		girls	$-7.24e^{-06}$	t(23.73) = 4.95	$4.85e^{-05}$	

Notes: PDS: Puberty Developmental Scale; DTI: Diffusion Tensor Imaging; GM: Grey Matter; WM: White Matter; FA: Fractional Anisotropy; MD: Mean Diffusivity.

3.3. Mediation analyses

Mediation analyses showed that amygdala volume change accounted for 32.5% (p = 0.024) and hippocampus volume change for 29.91% (p = 0.016) of the total effect between sex and "positive characteristics" along puberty (see Fig. 3, Table 5). Amygdala and hippocampus volumes increases in boys were related to "positive characteristics" increase, while amygdala and hippocampus volumes decreases in girls were related to "positive characteristics" decrease.

No mediation effect of the prefrontal cortex volume or of the uncinate and cingulum microstructural measures was found with YSI scores.

4. Discussion

Sexual differences of the brain maturation were identified in global GM and WM volumes and in regions of the amygdalo-hippocampal complex using a longitudinal multimodal neuroimaging approach in adolescents between 14 and 16 years. In contrast, no sexual difference of the microstructure maturation was detected. Additionally, we found sex differences on emotional regulation as measured by positive personality traits and this effect was related to the maturation of regions of the limbic system.

The sex effects on the adolescents' "positive characteristics" changes, that are a subscale of the positive personality traits scale, were identified

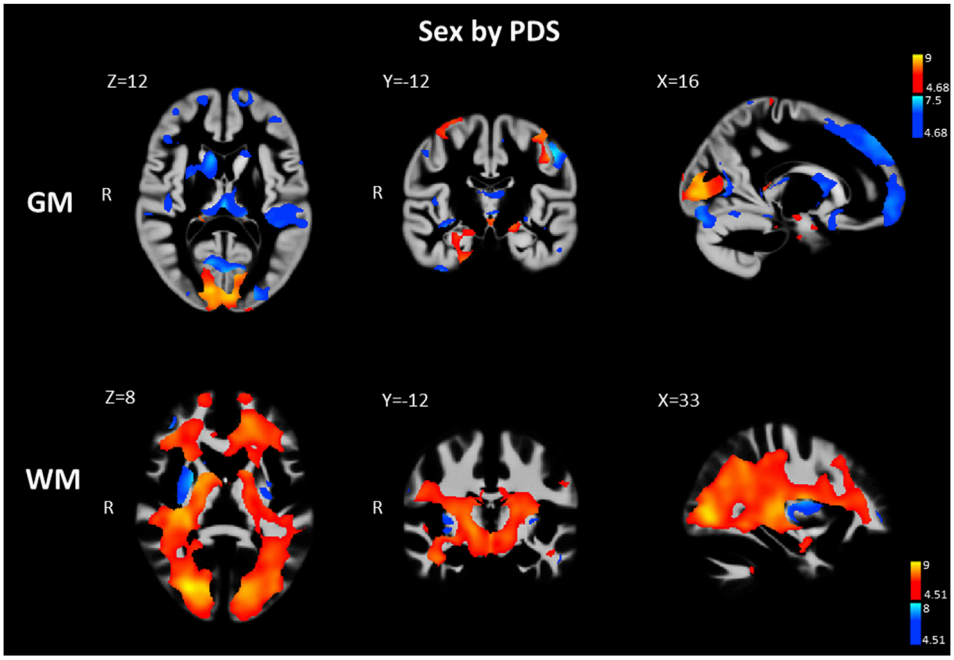

Fig. 2. Voxel-based sex-by-PDS interaction for GM (top row) and WM (bottom row). Steeper decreases in girls than boys in blue-light blue color scale and steeper increases in boys than girls in red-yellow color scale are superimposed on the sample mean GM and WM images. Color scales represent t-values ($p < 0.05$ FWE corrected). R: Right; PDS: Puberty Developmental Scale; GM: Grey Matter; WM: White Matter.

Table 4
Effects of PDS by sex on Region Of Interest measures.

imaging	measure	region	sex	change estimate (per PDS point)	*t*-test (degree of freedom)	p-value	interaction sex-by-PDS p-value
T1-weighted	GM (cm^3)	amygdala	boys	0.017	t(110.2) = 5.44	$3.24e^{-07}$	$4.89e^{-11}$
			girls	−0.015	t(110.5) = 4.55	$1.36e^{-05}$	
		hippocampus	boys	0.08	t(48.12) = 9.16	$4.02e^{-12}$	$3.17e^{-15}$
			girls	−0.02	t(46.84) = 3.20	0.0024	
		prefrontal cortex	boys	−0.52	t(2.17) = 2.28	0.13	$1.81e^{-07}$
			girls	−1.90	t(2.24) = 8.13	0.01	
DTI	FA	uncinate	boys	0.00031	t(2.10) = 1.70	0.22	0.079
			girls	−0.00071	t(2.32) = 0.39	0.72	
		cingulum	boys	0.012	t(1.22) = 2.72	0.18	0.053
			girls	0.018	t(1.26) = 3.95	0.11	
		cingulum (hippocampal)	boys	0.0056	t(1.15) = 0.97	0.49	0.052
			girls	$-6.22e^{-04}$	t(1.18) = 0.10	0.93	
	MD (10^{-3} mm^2/s)	uncinate	boys	$-8.42e^{-06}$	t(1.79) = 3.20	0.09	0.12
			girls	$4.37e^{-06}$	t(1.85) = 1.65	0.24	
		cingulum	boys	$-7.72e^{-06}$	t(5.18) = 4.85	0.0042	0.92
			girls	$-7.53e^{-06}$	t(5.39) = 4.65	0.0045	
		cingulum (hippocampal)	boys	$-1.04e^{-05}$	t(1.45) = 1.94	0.23	0.42
			girls	$-6.93e^{-06}$	t(1.50) = 1.28	0.36	

Notes: PDS: Puberty Developmental Scale; DTI: Diffusion Tensor Imaging; GM: Grey Matter; FA: Fractional Anisotropy; MD: Mean Diffusivity.

to be mediated by the hippocampus and amygdala maturation. Positive attributes are meant to gather (1) positive character items (e.g. how the adolescent feels generous, affectionate, caring, social, easy-going) and (2) positive action items (e.g. how the adolescent is proud to be good at sport, well behaved, polite, helpful at home). Globally, they are positively and closely related to current levels of adolescent's well-being (Gillham et al., 2011). "Positive characteristics" are assimilated to personality strengths that promote connections to other people which increase positive affect, suggesting that interpersonal interactions play an important role in the protection from depression (Gillham et al., 2011; Peterson and Seligman, 2004). In our sample, the "positive characteristics" correlated negatively with internalizing, externalizing and total difficulties scores (see Supplementary Table 11). Externalizing behaviors describe disruptive and dysregulated behaviors such as hyperactivity or impulsivity whereas internalizing problems involve disturbances in emotion or mood (Graber, 2013; Perle et al., 2013; Yong et al., 2014). In this context, positive personality traits may contribute to a decreased risk of developing emotional disorders during early adulthood, as demonstrated by Bromley et al., 2006 and Vidal-Ribas et al., 2015. The mediation by the amygdalo-hippocampal complex, limbic structures largely involved in the emotional regulation processing, has to be put in the light of the sex-related differences on the maturation of these regions (Davidson et al., 2002; Giedd, 2004; Goddings et al., 2014; Herting et al., 2018). In normal development, the amygdala and hippocampus continued to increase in volume during puberty in both boys and girls with differential trajectories (Goddings et al., 2014; Herting et al., 2018). Differences in the progression of brain structure could lead to important psychiatric disorders in post-adolescence, which prevalence is notable during this period (Lebel and Beaulieu, 2011; Paus et al., 2008). For example, variations of amygdala and hippocampus have been involved in affective

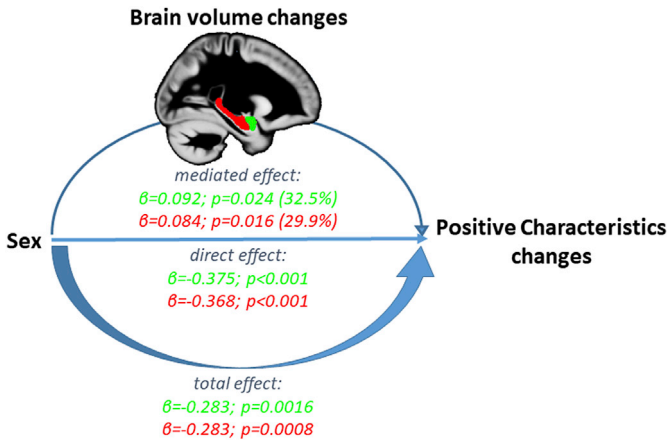

Fig. 3. Mediation of brain volume changes of the amygdala (in green) and the hippocampus (in red) on the relationship between sex and "positive characteristics" changes between 14 and 16 years using causal mediation analysis.

Table 5
Mediation of brain volume changes of the amygdala and the hippocampus on the relationship between sex and "positive characteristics" changes between 14 and 16 years using causal mediation analysis.

effect type	estimate	95% confidence	p-value
mediator variable: amygdala volume change			
mediation effect	0.092	[0.0082–0.21]	0.024
direct effect	−0.37	[-0.71 – -0.13]	$<2e^{-16}$
total effect	−0.28	[-0.54 – -0.09]	0.0016
proportion mediated	−0.32	[-0.86 – -0.04]	0.026
mediator variable: hippocampus volume change			
mediation effect	0.084	[0.017–0.16]	0.016
direct effect	−0.36	[-0.67 – -0.15]	$<2e^{-16}$
total effect	−0.28	[-0.55 – -0.09]	0.0008
proportion mediated	−0.29	[-0.91 – -0.06]	0.016

disorders, where volumes decreases were demonstrated in patients with emotional symptomatology compared to controls (Blumberg et al., 2003; Rajmohan and Mohandas, 2007). In summary, emotion dysregulation leading to emotional disorders is related to limbic system maturation, in particular amygdala and hippocampus changes during adolescence. According to our results, girls could be more sensitive to emotional disorders via positive personality traits and limbic structures volumes decreases, suggesting that a faster and precocious maturation during adolescence reflects a vulnerable framework for emotional dysregulation in early adulthood. As an echo to that, we did find a significant PDS related increase of risk for separation anxiety in girls only (See Supplementary Table 1). These elements taken together seem to point out an increased risk for psychopathology in early maturation in girls. Graber (2013) extended this relation in boys maturing too early or too late, which presented elevated symptomatology of psychopathology. As for boys, we did find that amygdalo-hippocampal complex increase was related to "positive characteristics" increase. Another study found that amygdala-mPFC connectivity related to early life stress in adolescence was associated with anxiety and depression in girls but again not in boys (Burghy et al., 2012). A long-standing explanation has been that men's more active responses to their negative moods may be more adaptive on average than women's less active, more ruminative responses (Nolen--Hoeksema, 1987). In our study, boys with no amygdalo-hippocampal complex increase could be considered as late maturing boys with no increase in positive attributes, which, in turn, may not be protective for developing psychopathology, contrary to boys with amygdalo-hippocampal complex and positive attribute increases. Otherwise, no sex-by-PDS interaction was detected, neither in the variables about affective disorders of the DAWBA questionnaire nor in the SDQ questionnaire. As only healthy adolescents were recruited in this study, the lack of pathological subjects might have decreased the statistical power of clinical variables to probe psychiatric dimensions.

The global patterns of brain maturation were confirmed in our study, with a global GM volume decrease and a global WM volume increase in macrostructure (Giedd et al., 1997), that might be an indication of a reduction in neuropil in the grey matter (e.g. synaptic pruning, glial cell reduction) and an encroachment of white matter growth (Mills et al., 2014; Paus et al., 2008). In microstructure, a global mean FA increase and a global mean MD decrease were found, suggesting more organized fiber bundles (Schmithorst and Yuan, 2010; Wang et al., 2012).

We confirmed the sexual differences of brain maturation illustrated by a steeper global GM volume decrease in girls and a steeper global WM volume increase in boys (Giedd et al., 1997; Goddings et al., 2014; Lenroot and Giedd, 2010). Regionally, the sexual differences were also confirmed in some specific regions as limbic regions and prefrontal cortex. These regions highlighted a sexual differentiation in maturation rates, with differential decreasing trajectories in prefrontal cortex volumes in boys and girls whereas trajectories were opposite in the amygdalo-hippocampal complex. According to the dual systems model, the prefrontal cortex involved in cognitive control follows a protracted development whereas limbic regions involved in processing affect follow a more dynamic model (Casey et al., 2008; Gogtay et al., 2004; Mills et al., 2014). In addition to confirming the differentiation in maturation rates between cortical and subcortical structures across puberty, we demonstrated that the sex plays an important role upon this mismatch. Through this design, we illustrated mainly a delayed maturation in boys and an accelerated maturation in girls. From one perspective, the relation in girls between what appears to be an accelerated amygdalo-hippocampal maturation and a decrease of "positive characteristics" could be interpreted as consistent with the dual system model where heightened reactivity of the subcortical regions would lead to more affectively driven behaviors and confer more risks for affective disorders (Casey et al., 2008). From another perspective, we did not find the same relation for the prefrontal cortex, the second system of the dual system model. In this case, our results could be consistent with an alternative model where vulnerability to affective disorders is not due to a delayed prefrontal maturation and a failure of regulation and controls over the subcortical system (Davey et al., 2008). From a general point of view, we can only consider our data in the context that a delayed and protracted maturation appears to be protective from emotional disorders.

No sex-by-PDS effect in the WM microstructural maturation between 14 and 16 was found, neither in whole brain nor limbic regions. Some studies have found sex-by-age interactions in FA from childhood to adulthood (Herting et al., 2017; Lebel and Beaulieu, 2011; Schmithorst et al., 2008; Wang et al., 2012). These longitudinal studies had smaller sample size (Bava et al., 2010; Wang et al., 2012) or larger age range (Lebel and Beaulieu, 2011), while others were cross-sectional (Herting et al., 2012). With its longitudinal design on a large sample, our study should have the computational strength to detect such changes. However, we did use pubertal development scale instead of age, since it is more closely related to brain maturation and that our age range is rather narrow (Goddings et al., 2014). As a confirmation, we did find sex differences for WM microstructural maturation when using age instead of PDS, but these results may be driven only by higher PDS increase for the same age range in boys as compared in girls giving in return an artificially sex-differential pace of brain maturation. Furthermore, brain maturation can be separated in distinct phases with rapid growth in childhood, followed by a slowing of growth in early–middle adolescence and an acceleration of growth again in late adolescence/early adulthood (Simmonds et al., 2014). The limbic system appears to follow this pattern of maturation, with cingulum and uncinate undergoing substantial changes after adolescence (Lebel and Beaulieu, 2011). This period of

little change that overlaps with our own study might account for the absence of significant sexual differences detected here on the WM maturation.

The longitudinal image processing and use of linear mixed-models specifically designed for repeated-measures constitute the main strengths of our study. Paired images underwent a dedicated processing pipeline to measure individual changes before performing spatial normalization and group analysis. In the first step of the model all time-points were registered to some form of within-subject average image, in order to avoid introducing an asymmetric bias and to ensure all images undergo the same number of interpolations (Ashburner and Ridgway, 2013; Reuter et al., 2012, 2010; Reuter and Fischl, 2011). This step is essential to guarantee the symmetry in the longitudinal processing. We were able to adapt our processing to diffusion images in order to adjust precisely both modalities in the same space. We used also appropriate statistical longitudinal models to take into account the dependence of repeated measurements within subject, and by doing so, providing increased statistical power reducing the confounding effect of between-subject variability (Bernal-Rusiel et al., 2013).

The findings of this study must be considered in the light of some limitations. First, we ran all our analyses using the pubertal development scale (PDS). First, it is a self-report measurement based on only five questions and can be prompted to subjectivity. Second, it measures not exactly the same physical characteristics in both sexes (e.g. breast development, testis size) which can bias the scale when comparing boys and girls brain maturations. In our study, we did not measure the Tanner stage where a clinician examines the participant and evaluates the degree of puberty (Marshall and Tanner, 1970, 1969). However, reliable studies have concluded that despite its limitations, PDS still constitutes a suitable tool to measure the degree of puberty (Bond et al., 2006; Dorn, 2006; Petersen et al., 1988) and remained useful and fundamental as predictor in assessing longitudinal changes within subjects, much more precise than age (Brooks-Gunn et al., 1987; Herting et al., 2017; Petersen et al., 1988). Given that girls in our sample have more advanced pubertal development than boys for the same age, our strategic choice seems to be the right one. Moreover, analyses conducted with age showed less significant results than with PDS within behavioral questionnaire and model fitting for the global T1-weighted measures was improved by adding the PDS.

In a second point regarding the temporal resolution, the current study had only two measures per subject, allowing for only a linear model to be examined as an estimate of change within a single individual (Herting et al., 2017). The two visits were close in time with a 2-year interval, necessary to detect subtle changes during puberty but maybe quite too narrow in view of changes during this period. Changes in brain maturation do not follow a linear curve; additional time points will allow the testing of non-linear slopes at the individual level and to detect medium effects of puberty. In the same vein considering the spatial resolution, we used a predefined set of brain ROI and, for example, the different subparts of the prefrontal region were not specifically considered in relation to their functions. Further investigations are needed to clarify the role of each region in the maturational mismatch of the limbic system.

The third limitation of this study is the use of Youth Strength Inventory questionnaire to study positive personality traits. Although part of the DAWBA, this questionnaire is often overlooked and not studied in the literature for symptomatology. Indeed, it is interesting that positive personality traits mirror emotional symptomatology in a study on healthy adolescents. Although being a self-report evaluation instead of a clinical measurement, it is, to our knowledge and available data, the only scale currently existing to measure positive personality traits subjectively. As an unexpected finding, externalizing and internalizing disorders and diagnoses scores of the DAWBA didn't show any interaction between sex and puberty but correlated negatively with the positive personality traits. This should be confirmed in future studies.

5. Conclusion

We demonstrated that the vulnerability of emotional disorders could be explained by the mismatch of maturation rates of cortico/subcortical regions between sexes across puberty. The delayed brain maturation in boys compared to girls showed to be related with positive personality traits changes. These findings support that, beyond age, sex and puberty effects contribute to neurodevelopmental trajectories and emotional regulation in girls and boys during adolescence.

Author contributions

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Gunter Schumann: Investigation, Project administration, Funding acquisition.

Michael N. Smolka: Investigation, Project administration, Funding acquisition.

Jean-Luc Martinot: Investigation,Conceptualization, Writing - Original Draft, Supervision, Funding acquisition.

Hervé Lemaître: Investigation, Conceptualization, Methodology, Software, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116441.

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