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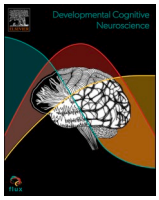

Sex differences in maturational timing of amygdala and prefrontal cortex volumes and white matter tract microstructure

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ABSTRACT

The developmental mismatch hypothesis (DMH) proposes that a mismatch in maturational timing of the amygdala and prefrontal cortex (PFC) drives adolescent sensation-seeking behaviour. While some studies provide support for the DMH, few have evaluated sex differences or examined both grey and white matter. Here, we used T1-weighted and diffusion-weighted magnetic resonance imaging (MRI) to examine amygdala and PFC macrostructure and amygdala-PFC white matter microstructure development across 606 MRI sessions from 148 typically developing children and adolescents (76 females) aged 1.95–17.71 years. Using generalized additive mixed effects models, we evaluated the maturational timing of amygdala volume, four PFC subregion volumes, and fractional anisotropy and mean diffusivity of the uncinate fasciculus and amygdala-PFC white matter tracts. Amygdala and PFC maturation was consistent with the DMH in males but less so in females. Relative to males, females exhibited less amygdala development and shorter periods of PFC development. In contrast to gray matter volumes, white matter changed continuously from early childhood to late adolescence, but ended earlier in females than in males. Our findings show different amygdala-PFC maturation patterns and that the amygdala-PFC neural system reaches maturity earlier in females than in males. These important differences may underlie sex differences in sensation-seeking behaviour.

1. Introduction

The timing of human brain development varies regionally (Konrad et al., 2013). Among many patterns, one is that subcortical regions develop earlier than cortical regions (Casey et al., 2008; Mills et al., 2014a; Shulman et al., 2016; Somerville et al., 2009). The developmental mismatch hypothesis (DMH) proposes that the difference in maturational timing between the amygdala and prefrontal cortex (PFC) is most prominent in early adolescence when amygdala development plateaus and PFC development accelerates (Casey et al., 2008; Mills et al., 2014a; Shulman et al., 2016; Somerville et al., 2009; Steinberg, 2008). Functional magnetic resonance imaging (MRI) research suggests that during adolescence, early maturing subcortical systems underlying reward-seeking behaviour have higher functional activation during emotion and reward processing compared to the slower-to-mature cortical systems that regulate executive functions and higher-order cognition (Ernst et al., 2005; Galvan et al., 2006; Geier et al., 2010). This mismatch may result in elevated emotion and reward system activation (Galván, 2010; Mills, et al., 2014a; Shulman et al., 2016). The DMH implicates elevated amygdala functional activation and reduced PFC functional activation in the development of normative sensation-seeking behaviours, especially in adolescence (Casey et al., 2008; Mills et al., 2014a; Shulman et al., 2016; Somerville et al., 2009; Steinberg, 2008).

Amygdala volume increases rapidly in early childhood and begins to plateau during late childhood and adolescence (Alex et al., 2024; Dima et al., 2021; Russell et al., 2021; Uematsu et al., 2012), though some work has suggested that amygdala volume may increase up to 20 years of age (Frere et al., 2020; Goddings et al., 2014; Mills, et al., 2014a; Thompson et al., 2020; Wierenga et al., 2014). On the other hand, PFC volume generally follows an inverted U-shaped trajectory, increasing rapidly early in life and then gradually decreasing between 6 and 30

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years (Amlien et al., 2016; Bethlehem et al., 2022; Brain Development Cooperative Group, 2012; Brown and Jernigan, 2012; Frere et al., 2020; Giedd et al., 1999; Kelly et al., 2024; Koolschijn and Crone, 2013; Lenroot et al., 2007; Mills, et al., 2014a, 2014b; Remer et al., 2017; Sowell et al., 1999; Tamnes et al., 2017; Villa et al., 2021). Voxel-based cortical volume studies suggest that PFC development is relatively uniform, with PFC subregions exhibiting similar rates of change (Amlien et al., 2016; Brown and Jernigan, 2012; Tamnes et al., 2017). However, some studies have reported that specific subregions, such as the frontal pole and orbital frontal cortex, show earlier volume decreases than the rest of the PFC (Amlien et al., 2016; Brown and Jernigan, 2012; Vijayakumar et al., 2016). While early amygdala and protracted PFC changes support the DMH and have been widely reported, these trends have rarely been compared using the same dataset. Further, many prior studies are cross-sectional, which can bias estimates of change over time (Horga et al., 2014). Additionally, previous longitudinal work has used models that assume linear, quadratic, or cubic trajectories. Newer models that fit non-linear trajectories with varying degrees of wiggliness can capture nuanced age-related changes in brain metrics and estimate rates of change at specific ages (McCormick et al., 2023).

The amygdala and PFC are connected by two primary white matter pathways: the uncinate fasciculus and amygdala-PFC tracts (Fig. 2; Fields, 2010). The uncinate fasciculus connects the inferior frontal gyrus, frontal pole, and orbital frontal cortex to the anterior temporal lobes by passing through the amygdala (Ebeling and von Cramon, 1992; Kier et al., 2004). The amygdala-PFC tract passes laterally through the superior internal capsule from the amygdala and terminates in the middle frontal gyrus, inferior frontal gyrus, frontal pole, and orbital frontal cortex (Hay et al., 2019). The uncinate fasciculus has one of the most prolonged developmental trajectories of the major white matter tracts, undergoing fractional anisotropy (FA) increases and mean diffusivity (MD) decreases past 25 years of age (Asato et al., 2010; Chen et al., 2016; Jáni et al., 2024; Lebel et al., 2008, 2012; Simmonds et al., 2014); in contrast, amygdala-PFC tract microstructure development has not been characterized. These connections are critical for amygdala-PFC communication, with prior multimodal work reporting a negative relationship between amygdala-PFC structural connectivity, as measured by FA and connectivity probability values, and amygdala functional activation during an emotion recognition task (Goetschius et al., 2019; Swartz et al., 2014). Low amygdala-PFC white matter FA and connectivity probability values have also been associated with increased amygdala-driven internalizing behaviours like anxiety (Eden et al., 2015; Greening and Mitchell, 2015; Kim and Whalen, 2009; Swartz et al., 2014). Although white matter microstructure development has been proposed to contribute to sensation-seeking behaviour in DMH literature (Steinberg, 2008), uncinate fasciculus and amygdala-PFC tract changes have not been investigated in a broad longitudinal sample, and have not been evaluated in conjunction with amygdala and PFC volumes.

Larger amygdala and PFC volumes in males than females have been

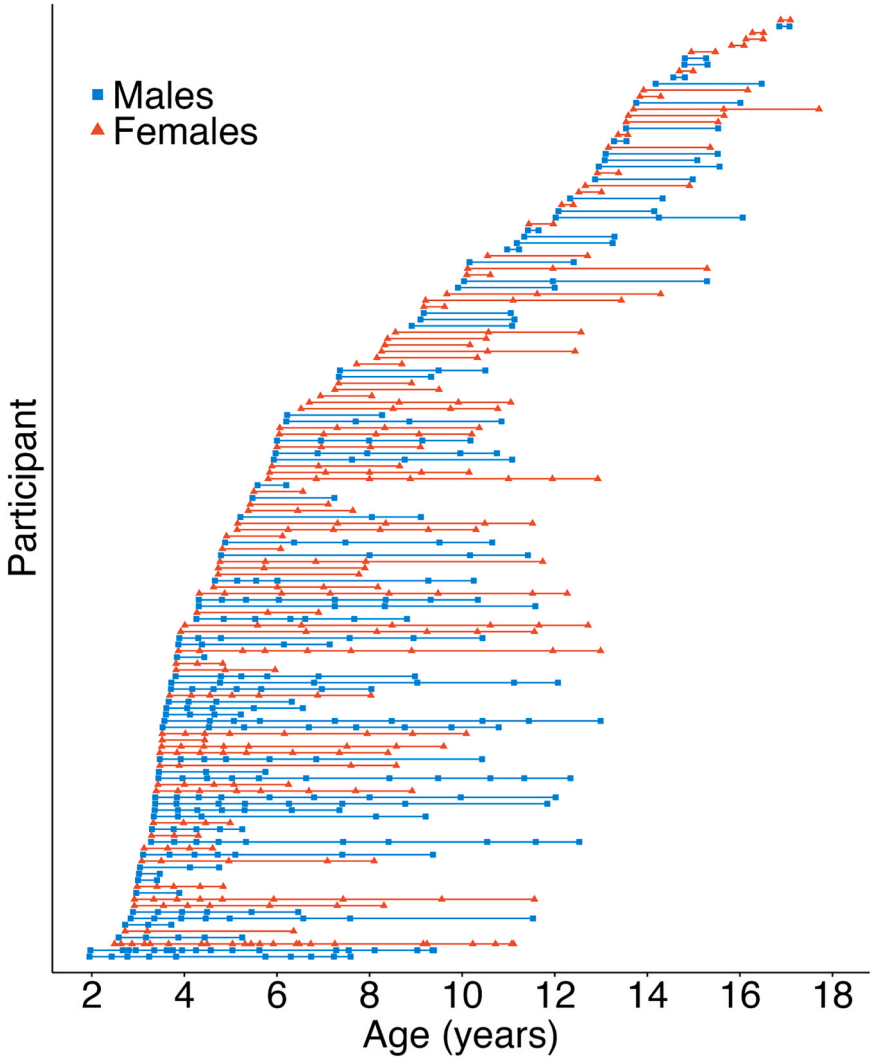

Fig. 1. Age at scan for all participants. Each line represents a participant, and each shape represents a participant's scan session included in the sample.

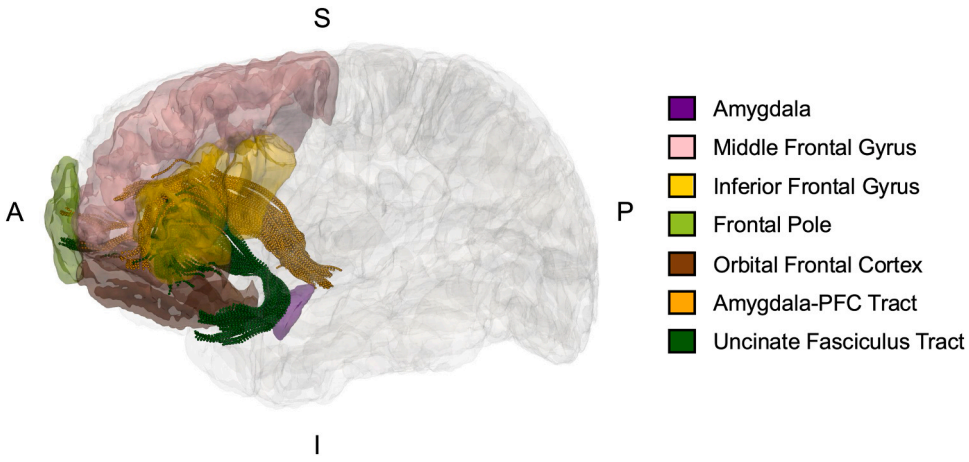

Fig. 2. Lateral view of the five grey matter regions and two reconstructed white matter tracts of interest (left hemisphere shown, but both hemispheres were measured) of a 3.74-year-old female participant (A = anterior, P = posterior, S = superior, I = inferior).

observed with and without intracranial volume (ICV) corrections (Goddings et al., 2014; Kelly et al., 2024; Koolschijn and Crone, 2013; Long et al., 2024; Mills et al., 2014b; Uematsu et al., 2012). Similarly, males have higher mean uncinate fasciculus FA than females (Kierońska et al., 2020; Lebel et al., 2012; Lebel and Beaulieu, 2011). Few studies have investigated sex differences in maturational timing; however, a handful show earlier amygdala volume growth in females compared to males (Goddings et al., 2014; Uematsu et al., 2012). Prior research on the PFC has been mixed, with some studies reporting that female frontal grey matter volumes peak and plateau earlier than males (Giedd et al., 1999; Lenroot et al., 2007; Remer et al., 2017; Tanaka et al., 2012), and others reporting no sex differences in PFC volume development (Mills et al., 2014b). Some studies have noted more protracted trajectories of uncinate fasciculus FA and MD in males (Clayden et al., 2012; Wang et al., 2012), while others have reported no sex differences (Frere et al., 2020; Krogsrud et al., 2016; Lebel et al., 2008, 2012; Lebel and Beaulieu, 2011; Muftuler et al., 2012; Simmonds et al., 2014). Further research is needed to clarify the effects of sex on the timing of brain development because they may drive sex differences in behaviours, such as sensation-seeking and impulsivity, which peak later and manifest more prominently in males than females (Shulman et al., 2015; Siraj et al., 2021).

A longitudinal study of 33 typically developing participants aged 7–30 years showed that amygdala volume stabilized earlier than PFC volume at both group and participant levels, indicating a developmental mismatch (Mills et al., 2014a). This mismatch was not related to retrospective reports of adolescent sensation-seeking behaviour collected in adulthood, and sex differences in trajectories were not examined. Another longitudinal study of 335 typically developing participants aged 14–16 years showed faster amygdala volume increases in males and slower PFC volume decreases in females (Frere et al., 2020). No sex-by-age interactions were observed in uncinate fasciculus and cingulum FA or MD (Frere et al., 2020). While sex differences in externalizing and internalizing behaviours were not observed, sex differences in positive personality traits such as generosity, caring, and affection were mediated by amygdala volume (Frere et al., 2020). These studies highlight the existence of developmental mismatches but point to the need for further investigation of sex differences across childhood and adolescence to better understand how brain development may influence behaviour.

The present study used a large longitudinal dataset, two MRI modalities, and advanced non-linear modelling to investigate amygdala and PFC (middle frontal gyrus, inferior frontal gyrus, frontal pole, orbital frontal cortex) volume, and uncinate fasciculus, and amygdala-PFC tract FA and MD developmental mismatches in females and males aged 1.95–17.71 years. We hypothesized that, in both sexes, amygdala and PFC volume maturational timing would be mismatched, with early amygdala volume increases in childhood and later PFC volume decreases in adolescence. We also expected amygdala-PFC white matter to follow a different maturational timing pattern from volume, with FA increasing and MD decreasing across childhood and adolescence. Additionally, we hypothesized that, compared to males, females would develop faster and plateau earlier in all metrics.

2. Methods

2.1. Participants

This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB23–0757). Typically developing child and adolescent MRI data were combined from four longitudinal studies conducted in Calgary, Alberta. Dataset 1 (92 participants/481 MRI sessions) was a longitudinal cohort study of typically developing participants recruited between ages 2–6 years who underwent MRI and cognitive assessments (Reynolds et al., 2020). Participants provided longitudinal data at intervals of 6–36 months until later childhood or early adolescence (up to 12 years of age) (Reynolds et al., 2020). Participants were identified as female or male based on their medical records. Dataset 2 (26 participants/60 MRI sessions) was a longitudinal cohort study of typically developing participants recruited between ages 6–15 years who underwent MRI and cognitive assessments (Geeraert et al., 2020). Some participants returned 2 and/or 4 years later to provide longitudinal data (6–17 years of age). Participant parents/guardians reported if their child was female or male. Dataset 3 (9 participants/23 MRI sessions) is an ongoing longitudinal cohort study of children and youth with prenatal alcohol exposure, as well as unexposed controls, who were recruited between 7 and 18 years of age and undergo MRI every 24 months and cognitive assessments every 12 months (Lebel et al., 2021); only unexposed controls were included here. Participant parents/guardians reported if their child was female or male. Dataset 4 (21 participants/42 MRI sessions) was a longitudinal cohort study of mild traumatic brain injury and orthopedic injury participants aged 8–17 years who underwent MRI and cognitive assessments within 10 days post-injury and at either 3- or 6-months post-injury (Yeates et al., 2017); only orthopedic injury controls were included here. Participants were identified as female or male based on parent reports of sex at birth.

All participants were born after 34 weeks gestation, free from genetic and neurodevelopmental disorder diagnoses at the time of recruitment, and had no contraindications for MRI scanning. Parent/guardian written informed consent was obtained for all participants. When possible, child

assent was also obtained. The sample included 148 participants (76 females) with 606 longitudinal scan sessions (range 2–23 sessions/participant, average 4.09 sessions/participant) with good quality T1-weighted and diffusion-weighted images collected across 1.95–17.71 years of age (Fig. 1). Males and females were well-matched across the age span. The average interscan interval was 1.09 years. Demographic characteristics are listed in Table 1 and Supplementary Table 1.

2.2. Magnetic resonance imaging acquisition

All four datasets were collected at the Alberta Children's Hospital using the same research-dedicated 3 T General Electric MR750w scanner with a 32-channel head coil. The MRI protocols are outlined in Table 2. Participants were not sedated and either slept naturally or watched a movie of their choice.

2.3. Image processing

2.3.1. T1-weighted images

N4 bias correction (Tustison et al., 2010) and 1 mm isotropic voxel size resampling (Cox, 1996) were performed on all T1-weighted images. Images were segmented using the Multi-atlas Cortical Reconstruction Using Implicit Surface Evolution (MaCRUISE) pipeline at the Vanderbilt University Institute of Imaging Science, Center for Computational Imaging (Huo et al., 2016a, 2016b). MaCRUISE integrates cortical reconstruction and multi-atlas segmentation to produce reliable and consistent cortical surface parcellations in anatomical agreement with brain segmentation across a broad age range (Huo et al., 2016a, 2016b; Long et al., 2024). Trained raters manually checked the T1-weighted images and refined segmentations for quality and accuracy per protocols outlined in previously published works (Long et al., 2024). Of the 789 successfully collected longitudinal scan sessions with T1 and diffusion-weighted images, 713 (90 %) sessions had good-quality T1-weighted images. Scan sessions with poorly rated T1-weighted images were excluded from our sample.

Longitudinal registration was performed to remove deviation from biological plausibility caused by additive effects of minor segmentation errors that may arise from the MaCRUISE pipeline and alter longitudinal trajectories on the participant level (Long et al., 2024). The T1-weighted image of a participant's middle scan (median scan age +/- 3 years) was registered to each of their other time points using a rigid, affine, and non-linear registration (NiftyReg—CMIC 2019). The resulting transformation fields were applied to the MaCRUISE segmentation of each participant's middle image to warp the middle segmentation into the native space of each previous and subsequent time point. Trained raters re-evaluated the longitudinally registered T1-weighted images and

Table 1
Sample demographics by sex. Two-sample *t*-test and Fisher's exact test results comparing sample demographics between females and males.

		Female (n = 76)	Male (n = 72)	*p*
Age (years)	Mean	7.91 + /- 3.63	7.35 + /- 3.61	.058
	Median	7.25	6.35	NA
	Minimum	2.49	1.95	NA
	Maximum	17.71	17.07	NA
Parental Marital Status	Single	5 (6.6 %)	6 (8.3 %)	.339
	Married/ Cohabitating	70 (92.1 %)	66 (91.7 %)	
	Not Reported	1 (1.3 %)	0	
Household Income ($CAD/year)	Less than 25,000	0	1 (1.4 %)	.944
	25,000–49,999	3 (3.9 %)	3 (4.2 %)	
	50,000–74,999	3 (3.9 %)	5 (6.9 %)	
	75,000–99,999	15 (19.7 %)	13 (18.1 %)	
	100,000–124,999	16 (21.1 %)	13 (18.1 %	
	125,000–149,999	5 (6.6 %)	4 (5.6 %)	
	150,000–174,999	8 (10.5 %)	7 (9.7 %)	
	More than 175,000	25 (32.9 %)	22 (30.6 %)	
	Not Reported	1 (1.3 %)	4 (5.6 %)	
Maternal Education	Some High School	1 (1.3 %)	1 (1.4 %)	.868
	High School Diploma	1 (1.3 %)	3 (4.2 %)	
	Some Postsecondary	4 (5.3 %)	3 (4.2 %)	
	Trade/Technical Diploma	17 (22.4 %)	12 (16.7 %)	
	Undergraduate Degree	32 (42.1 %)	30 (41.7 %)	
	Some Postgraduate	0	1 (1.4 %)	
	Postgraduate Degree	18 (23.7 %)	21 (29.2 %)	
	Not Reported	3 (3.9 %)	1 (1.4 %)	

Table 2
T1 and diffusion-weighted magnetic resonance imaging protocols. FSPGR BRAVO = Fast SPoiled GRadient echo BRAin VOlume Imaging; TR = repetition time; TE = echo time; TI = inversion time; SE-EPI = spin-echo echo planar imaging.

Dataset Number	T1-weighted Protocol		Diffusion-weighted Protocol	
Dataset 1	Sequence	FSPGR BRAVO	Sequence	SE-EPI
	Scan Time (min)	4:26	Scan Time (min)	4:03
	Resolution (mm^3)	0.9 × 0.9 × 0.9	Resolution (mm^3)	1.6 × 1.6 × 2.2
	TR (ms)	8.23	TR (ms)	6750
	TE (ms)	3.76	TE (ms)	79
	TI (ms)	540	Non-gradient Encoding Directions	5 interleaved images at $b = 0$ s/mm^2
	Flip Angle (degrees)	12	Gradient Encoding Directions	30 images at $b = 750$ s/mm^2
Dataset 2	Sequence	FSPGR BRAVO	Sequence	SE-EPI
	Scan Time (min)	5:38	Scan Time (min)	7:12
	Resolution (mm^3)	0.8 × 0.8 × 0.8	Resolution (mm^3)	2.2 × 2.2 × 2.2
	TR (ms)	8.25	TR (ms)	12,000
	TE (ms)	3.2	TE (ms)	88
	TI (ms)	600	Non-gradient Encoding Directions	5 interleaved images at $b = 0$ s/mm^2
	Flip Angle	10	Gradient Encoding Directions	30 images at $b = 900$ s/mm^2
Dataset 3	Sequence	FSPGR BRAVO	Sequence	SE-EPI
	Scan Time (min)	5:38	Scan Time (min)	7:08
	Resolution (mm^3)	0.8 × 0.8 × 0.8	Resolution (mm^3)	2.2 × 2.2 × 2.2
	TR (ms)	8.25	TR (ms)	13,500
	TE (ms)	3.2	TE (ms)	88
	TI (ms)	600	Non-gradient Encoding Directions	5 non-interleaved images at $b = 0$ s/mm^2
	Flip Angle	10	Gradient Encoding Directions	20 images at $b = 900$ s/mm^2
Dataset 4	Sequence	FSPGR BRAVO	Sequence	SE-EPI
	Scan Time (min)	5:38	Scan Time (min)	7:12
	Resolution (mm^3)	0.8 × 0.8 × 0.8	Resolution (mm^3)	2.2 × 2.2 × 2.2
	TR (ms)	8.25	TR (ms)	12,000
	TE (ms)	3.2	TE (ms)	88
	TI (ms)	600	Non-gradient Encoding Directions	5 interleaved images at $b = 0$ s/mm^2
	Flip Angle	10	Gradient Encoding Directions	30 images at $b = 900$ s/mm^2

segmentations for quality and accuracy per previously published protocols (Long et al., 2024). Of the 674 scan sessions with good quality longitudinally-registered T1-weighted and diffusion-weighted images (see diffusion-weighted image exclusion numbers in Section 2.3.2), 640 (95 %) had good quality longitudinally registered, refined segmentations. Longitudinally registered, refined segmentations with poor ratings were excluded from our final sample. 29 additional scan sessions were excluded from our final sample because, after T1 and diffusion-weighted exclusions, the data were cross-sectional and ineligible for our longitudinal sample. Using in-house MATLAB scripts, ICV and regional volumes (mm^3) were calculated from the good-quality segmentations in the native space of each time point. Left and right amygdala and PFC volume were used in analyses (Fig. 2). Four PFC subregions were evaluated: the middle frontal gyrus, inferior frontal gyrus, frontal pole, and orbital frontal cortex. Middle frontal gyrus and frontal pole volume were obtained from the single middle frontal gyrus and frontal pole MaCRUISE volumetric labels. The triangular, orbital, and opercular inferior frontal gyrus MaCRUISE volumetric labels were combined to create a single inferior frontal gyrus volume metric (Klein and Tourville, 2012). The anterior, lateral, medial, and posterior orbital frontal cortex MaCRUISE volumetric labels were combined to create a single orbital frontal cortex volume metric (Rolls et al., 2015).

2.3.2. Diffusion-weighted images

Trained raters manually quality-checked raw diffusion-weighted images following previously published methods (Reynolds et al., 2019a). Of the 789 successfully collected longitudinal scan sessions with T1-weighted and diffusion-weighted images, 750 (95 %) sessions had good-quality diffusion-weighted images. Scan sessions with poorly rated diffusion-weighted images were excluded from our final sample. Using ExploreDTI (Leemans et al., 2009), each image from datasets 1, 2, and 4 was flipped and permutated into a uniform orientation and corrected for signal drift, Gibbs ringing effects, participant motion, and eddy current distortions. Images from dataset 3 underwent the same preprocessing steps except for signal drift correction, which was not performed because the dataset had non-interleaved $b = 0$ s/mm^2 images, preventing signal drift magnitude estimation (Hansen et al., 2018). For each image, whole-brain deterministic fibre tractography was performed to reconstruct all the white matter tracts in the brain using a minimum FA threshold of 0.15 and an angle threshold of 30°. Semi-automated tractography isolated the uncinate fasciculus and amygdala-PFC tracts in the left and right hemispheres of each image (Fig. 2) (Hay et al., 2019; Reynolds et al., 2019b). Tract quality was manually assessed, and additional exclusion criteria were added on a tract-by-tract basis to eliminate spurious fibres. Average FA and MD were calculated for each tract for each participant.

2.4. Metric harmonization

Metric harmonization and statistical analyses were performed in RStudio (R version 4.3.2; RStudio version 2023.06.0 +421) (Posit Team, 2023). To account for differences in brain metrics caused by variations in scan sequences, ComBat Harmonization was performed separately for left and right regional volumes, FA, and MD values (R package *neuroCombat* version 1.0.13) (Fortin et al., 2017, 2018; Johnson et al., 2007). In ComBat Harmonization models for T1-weighted image metrics, data were grouped based on protocol sequence and a batch term of two was used ("scanner 1" = dataset 1, "scanner 2" = datasets 2, 3, 4). In ComBat Harmonization models for diffusion-weighted image metrics, data were grouped based on protocol sequence and a batch term of three was used ("scanner 1" = dataset 1, "scanner 2" = datasets 2 and 4, "scanner 3" = dataset 3). A covariate matrix with age at scan and sex was included in each model to preserve biological variability in the data (Fortin et al., 2017). The empirical Bayes estimation option was not applied (eb = FALSE) because each metric was harmonized separately (number of features < scans) (Onicas et al. 2022b). For each metric, the following model was used to harmonize the data:

neuroCombat(dat = Metric, batch = Scanner, mod = mod, eb = FALSE)

Values four standard deviations above or below the group mean of each metric were identified and deemed outliers. One FA value and four MD values from different scan sessions and participants were identified. Any scan session with an outlier value was excluded from the sample to ensure all final scan sessions had good quality and non-outlier volume, FA, and MD data. One additional scan session was removed because the participant no longer had longitudinal data after outlier removal.

2.5. Statistical analysis

Two-sample *t*-tests and Fisher's exact tests were performed to test sex differences in mean age, parental marital status, household income, and maternal education.

Volume, FA, and MD values were standardized to z-scores across the study cohort (R package *base*) (R Core Team, 2023). Standardized volume, FA, and MD developmental trajectories were modelled using generalized additive mixed effects models (GAMMs) (R package *mgcv* version 1.9.0) (Wood, 2004, 2017). GAMMs use splines to fit linear and non-linear relationships between predictors (i.e., age) and response variables (i.e., volume, FA, MD) (McCormick et al., 2023). GAMMs correlate observations obtained from the same participant equally and can model longitudinal data obtained at varying intervals and over different age ranges (McCormick et al., 2023). We used the following model to fit developmental trajectories of left and right standardized volume, FA, and MD:

gamm(Standardized Metric ~ s(Age), method = "REML", random = list(Participant = ~1))

Male and female trajectories were fit separately. While directly testing interactions within one model would be ideal, this is currently not feasible within GAMMs. Ordered factor (by=) smooth interaction terms weight overall fit lines by all levels, meaning that female and male basis functions would be weighted using data from the opposite sex. Factor smooth (bs = "fs") interaction terms are designed to fit a large number of random smooths and would force female and male trajectories to have the same degree of wiggliness, which does not align with our hypotheses (Pederson et al., 2019). All GAMMs contained a smoothed age term and random effect term to account for longitudinal data. Each GAMM had a fixed overall intercept and a random intercept per participant. All volume models contained a covariate term for ICV, calculated by summing all 132 MaCRUISE regional volume values. ICV was included in each model to account for within-sex differences in head size. The basis function (k) of the s(age) term in each model was manually selected by starting at k = 4 and increasing k until the effective degrees of freedom stopped changing (Schoenig et al., 2023). Restricted maximum likelihood (REML) was used when fitting all models. For all trajectories, age ranges with significant changes were identified by calculating the 95 % confidence intervals of the first derivative of each GAMM trendline (R package *stats*) (R Core Team, 2023). Age ranges undergoing significant change were identified when the 95 % confidence intervals of the first derivative did not include zero (R package *gratia* version 0.8.1) (Jalbrzikowski et al. 2022b; Larsen et al., 2020; Simpson, 2018, 2023). Two sample *t*-tests were used to test for sex differences between the average rate of change calculated within overlapping periods of significant change for each metric. False discovery rate correction at $q < .05$ was used to correct for 16 two-sample *t*-test rate of change comparisons.

A supplementary analysis was performed to examine sex differences in axial diffusivity (AD) and radial diffusivity (RD) of the uncinate fasciculus and amygdala-PFC tracts. Average AD and RD values were calculated for each tract in the left and right hemispheres of each image. GAMMs were rerun with AD and RD as dependent variables. AD and RD rates of change and periods of significant change were calculated.

3. Results

Males and females did not differ in demographic characteristics (Table 1). Fig. 3 depicts the standardized volume, FA, and MD trajectories, rates of change, and periods of significant development for females and males. GAMM model summary information and average rate of change comparison results are described in Supplementary Tables 2 and 3.

3.1. Relative to males, females show less amygdala volume development

Females showed no significant age-related changes in left amygdala volume, and increases in right amygdala volume only between 6.5 and 8.7 years (Fig. 3). Males showed significant age-related increases in left amygdala volume between 6.3 and 9.4 years, and in right amygdala volume between 2.0 and 4.1 years and 6.6–8.7 years. For right amygdala volume, females had a significantly faster rate of change (0.211 z-score/year) than males (0.191 z-score/year) ($p = .005$, $q = .008$).

3.2. Relative to males, females exhibit shorter periods of significant PFC development

Females exhibited significant age-related decreases in left and right middle frontal gyrus volume between 6.1 and 15.1 years and 6.9–11.1 years, respectively, whereas males exhibited decreases between 6.4 and 16.0 years and 6.5–15.6 years, respectively (Fig. 3). Females (left = −0.093 z-score/year; right = −0.100 z-score/year) demonstrated significantly faster decreases in both left and right middle frontal gyrus volume than males (left = −0.078 z-score/year; right = −0.086 z-score/year) (left, $p < .001$, $q < .001$; right, $p < .001$, $q < .001$).

Females exhibited significant age-related decreases in left and right inferior frontal gyrus volume between 6.6 and 11.9 years and 7.9–12.6 years, respectively, while males showed decreases in left inferior frontal gyrus volume between 2.0 and 14.8 years. Males showed no significant age-related changes in right inferior frontal gyrus volume. Females (-0.071 z-score/year) had significantly faster decreases in left inferior frontal gyrus volume than males (-0.058 z-score/year) ($p < .001$, $q < .001$).

Females displayed significant age-related decreases in left and right orbital frontal cortex volume between 2.5 and 17.7 years and 14.0–17.7 years, respectively. Males exhibited significant decreases in left orbital frontal cortex volume between 2.0 and 6.7 years and 11.2–17.1 years, and in right orbital frontal cortex volume between 2.9 and 6.2 years and 12.1–16.8 years. Males (-0.106 z-score/year) demonstrated a significantly faster decrease in left orbital frontal cortex volume than females (-0.021 z-score/year) ($p < .001$, $q < .001$). Females (-0.136 z-score/year) had faster right orbital frontal cortex volume decreases than males (-0.111 z-score/year) ($p < .001$, $q < .001$).

Females showed significant age-related decreases in left and right frontal pole volume between 5.9 and 11.9 years and 6.2–10.0 years, respectively, whereas males exhibited decreases between 2.0 and 17.1 years and 6.0–17.1 years, respectively. Females (left = −0.091 z-score/year; right = −0.075 z-score/year) had significantly faster decreases in both left and right frontal pole volume than males (left = −0.046 z-score/year; right = −0.039 z-score/year) (left, $p < .001$, $q < .001$; right, $p < .001$, $q < .001$).

3.3. Relative to males, females show earlier amygdala-PFC white matter development

Females exhibited significant age-related increases in left and right uncinate fasciculus FA between 2.5 and 12.1 years and 2.5–8.0 years, respectively, while males showed increases between 2.0 and 15.6 years and 2.0–15.0 years, respectively (Fig. 3). Left uncinate fasciculus FA rates of change did not differ between females (0.223 z-score/year) and males (0.227 z-score/year) ($p = .788$, $q = .788$). Females (0.284 z-score/year) had significantly faster increases in right uncinate fasciculus FA than males (0.229 z-score/year) ($p < .001$, $q < .001$).

Females showed significant age-related decreases in left uncinate fasciculus MD between 2.5 and 8.0 years and 11.9–12.7 years, and in right uncinate fasciculus MD between 2.5 and 9.7 years. Males displayed decreases in left and right uncinate fasciculus MD decreases between 2.0 and 8.5 years and 2.0–8.9 years, respectively. Females (-0.421 z-score/year) demonstrated a significantly faster decrease in left uncinate fasciculus MD than males (-0.342 z-score/year) ($p < .001$, $q < .001$). Right uncinate fasciculus MD rates of change did not differ between females (-0.287 z-score/year) and males (-0.256 z-score/year; $p = .014$, $q = .021$).

Females demonstrated significant age-related increases in left and right amygdala-PFC FA between 2.5 and 10.2 years and 2.5–15.8 years, respectively, while males showed significant increases between 2.0 and 14.7 years and 2.0–14.3 years, respectively. Left and right amygdala-PFC tract FA rates of change did not differ between females (left = 0.208 z-score/year; right = 0.222 z-score/year) and males (0.205 z-score/year; right = 0.229 z-score/year) (left, $p = .756$, $q = .788$; right, $p = .420$, $q = .480$).

Females exhibited significant age-related decreases in left and right amygdala-PFC MD between 2.5 and 9.8 years and 2.5–14.1 years, respectively. Males showed significant decreases in left and right amygdala-PFC MD between 2.0 and 11.1 years and 2.0–10.0 years, respectively. Left and right amygdala-PFC tract MD rates of change did not differ between females (left = −0.249 z-score/year; right = −0.285 z-score/year) and males (-0.233 z-score/year; right = −0.272 z-score/year) (left, $p = .103$, $q = .137$; right, $p = .211$, $q = .259$).

3.4. Supplementary analyses

Females exhibited significant age-related decreases in left uncinate fasciculus AD between 2.6 and 7.5 years and increases between 9.2 and 10.0 years. Females also had right uncinate fasciculus AD decreases between 2.5 and 11.4 years. Males showed left and right uncinate AD decreases between 2.7 and 8.3 years and 2.0–9.9 years, respectively. Females showed significant age-related decreases in left uncinate fasciculus RD between 2.5 and 8.4 years and 11.7–12.7 years, and in right uncinate fasciculus RD between 2.5 and 8.9 years. Males displayed decreases in left uncinate fasciculus RD between 2.0 and 8.8 years and 11.5–14.2 years. Males also showed right uncinate RD decreases between 2.0 and 13.9 years.

Females demonstrated significant age-related decreases in left and right amygdala-PFC tract AD between 2.5 and 15.3 years and 2.5–17.7 years, respectively, while males showed significant decreases between 2.0 and 12.7 years and 4.2–5.6 years, respectively. Females exhibited significant age-related decreases in left and right amygdala-PFC tract RD between 2.5 and 17.7 years and 2.5–16.3 years, respectively. Males showed significant decreases in left and right amygdala-PFC tract RD between 2.0 and 15.7 years and 2.0–13.1 years, respectively (Supplementary Figure 1).

4. Discussion

In this large longitudinal study of typically developing children and adolescents, we show that the maturational timing of the amygdala and PFC proposed in the DMH holds in males but is less apparent in females. Females exhibit fewer and shorter periods of amygdala and PFC volume development than males. We also showed that amygdala-PFC white matter microstructure development ends earlier in females than in males. Our findings have implications for understanding behavioural differences between females and males across childhood and adolescence.

Our work illustrates two mismatches, or differences, in maturational timing: one between amygdala and PFC volumes and another between grey matter volumes and amygdala-PFC white matter microstructure.

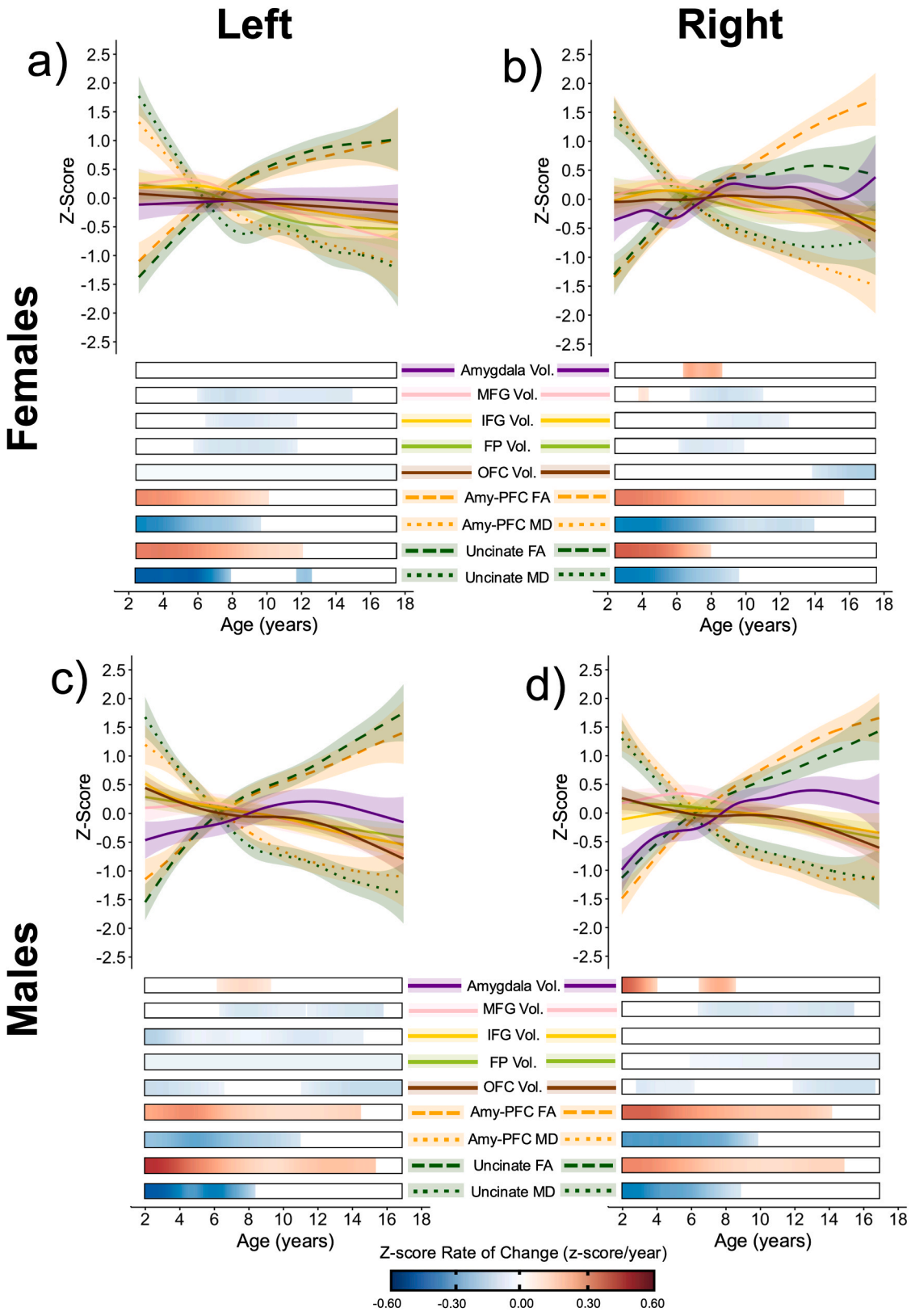

Fig. 3. Amygdala and prefrontal cortex (middle frontal gyrus (MFG), inferior frontal gyrus (IFG), frontal pole (FP), orbital frontal cortex (OFC)) volume and uncinate fasciculus and amygdala-PFC tract fractional anisotropy (FA) and mean diffusivity (MD) trajectories in a) female left hemisphere, b) female right hemisphere, c) male left hemisphere, and d) right male hemisphere). Combined z-score trajectories with 95 % confidence intervals are shown. Coloured bars reflect metric rates of change (z-score/year; blue=decrease, red=increase); white portions represent periods when significant change did not occur. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Regardless of sex, we observed amygdala volume increases until late childhood and PFC volume decreases through adolescence. These trends align with the DMH, showing that the amygdala reaches a developmental plateau before the PFC in typically developing individuals. Our findings align with previous work demonstrating amygdala volume increases in childhood (Alex et al., 2024; Dima et al., 2021; Russell et al., 2021; Uematsu et al., 2012) and PFC volume decreases into adolescence and adulthood (Amlien et al., 2016; Bethlehem et al., 2022; Brain Development Cooperative Group, 2012; Brown and Jernigan, 2012; Lenroot et al., 2007; Mills et al., 2014a, 2014b; Sowell et al., 1999). Although macrostructural measures like volume and microstructural processes are difficult to link in living humans, age-related subcortical volume increases are thought to be related to synaptogenesis, neuronal proliferation and migration, which preclinical models have shown to dominate early life and form new connections in the brain (Stiles and Jernigan, 2010). Age-related cortical volume decreases are associated with synaptic and neuronal pruning and dendritic reorganization, which increase in adolescence in preclinical models and refine and strengthen neuronal connections (Kolk and Rakic, 2022; Markham et al., 2007). Future studies using methods that evaluate cortical microstructure can disentangle how grey matter architecture changes relate to volume growth. In both sexes, uncinate fasciculus and amygdala-PFC tract FA increased and MD decreased, changing rapidly in early childhood, more gradually in middle childhood to early adolescence, and beginning to plateau in middle to late adolescence. Our findings suggest that the uncinate fasciculus and amygdala-PFC tracts have similar patterns of maturational timing and are not fully matured by the start of adolescence. Age-related white matter microstructure changes are attributed to myelination and axonal packing, which are prolonged processes (Lebel and Deoni, 2018). Our findings align with previous evidence that tracts projecting to the frontal lobe have particularly prolonged trajectories (Asato et al., 2010; Chen et al., 2016; Lebel et al., 2008, 2012; Lebel and Beaulieu, 2011; Lynch et al., 2020; Simmonds et al., 2014). However, we did not observe significant changes in FA and MD between 16 and 18 years of age, in contrast to previous work showing changes in uncinate fasciculus microstructure past 25 years of age (Asato et al., 2010; Chen et al., 2016; Jáni et al., 2024; Lebel et al., 2008, 2012; Simmonds et al., 2014). Narrower windows of change may reflect flatter trajectories at older ages due to sparser data or methodological differences; we identified periods of significant change statistically, while previous work has relied on qualitative descriptions of overall trends and percent change. As previous literature suggests that PFC subregions (Amlien et al., 2016; Bethlehem et al., 2022) and white matter tracts, including the uncinate fasciculus (Asato et al., 2010; Chen et al., 2016; Jáni et al., 2024; Lebel et al., 2008, 2012; Simmonds et al., 2014) develop into the third decade of life, mismatches in maturational timing may persist longer than shown here. Future studies with broader aged samples can apply our methods to elucidate if and how these structures continue changing.

We found sex differences in model wiggliness and maturational timing, with the developmental mismatch being more apparent in males than females. While males showed significant left amygdala growth from middle to late childhood and right amygdala growth from early to late childhood, females displayed no significant left amygdala volume changes and right amygdala growth only from middle childhood until late childhood. These findings support previous reports of amygdala trajectory lateralization showing earlier and more protracted changes in the right amygdala than the left amygdala (Russell et al., 2021; Uematsu et al., 2012). Our findings are similar to previous work showing that females undergo fewer amygdala volume changes than males (Goddings et al., 2014). Previous research evaluating sex differences in trajectory peaks has reported that female amygdala volumes peak before males (Goddings et al., 2014; Uematsu et al., 2012). However, our findings suggest that female and male amygdala volumes begin stabilizing around the same time (~8–9 years). Compared to males, females exhibited shorter periods of PFC volume development that ended earlier than males. Males showed significant PFC volume development from early childhood until late adolescence. Female PFC volumes began significantly changing in middle to late childhood and stopped by early to middle adolescence. The PFC maturational timing we observed in males is more similar to prior work in combined female and male samples, showing PFC volume changes into adulthood (Amlien et al., 2016; Brown and Jernigan, 2012; Mills et al., 2014a, 2014b; Sowell et al., 1999). Less female representation (~30–43 % female) in prior studies may explain why the trajectories of some combined samples are skewed toward the maturational timing of males (Mills et al., 2014a, 2014b). Even in studies with equal female and male representation (~46–53 % female), averaged findings across sexes may have obscured sex-specific patterns (Amlien et al., 2016; Brown and Jernigan, 2012; Sowell et al., 1999). Our observation of earlier PFC maturation in females aligns with work that examined females and males separately (Brain Development Cooperative Group, 2012; Frere et al., 2020; Lenroot et al., 2007; Raznahan et al., 2010; Remer et al., 2017). While a developmental mismatch was still observed in females, the difference between the endpoints of significant amygdala and PFC development was smaller in females than in males, indicating a less pronounced mismatch. Interestingly, in males, frontal pole and orbital frontal cortex volumes continued to undergo significant change until the end of our sample's age range, past when the middle frontal gyrus and inferior frontal gyrus stopped changing. With the exception of right orbital frontal cortex volume, this trend was not seen in females. These results suggest that males have amygdala-frontal pole and amygdala-orbital frontal cortex mismatches that are particularly large compared to their female counterparts. Given the orbital frontal cortex and frontal poles' critical role in emotion and reward processing and future planning, prolonged development in these areas in males may have behavioural implications (Bludau et al., 2014; Dixon et al., 2017). Our work highlights the importance of considering sex-specific trajectories in developmental studies.

In both sexes, the uncinate fasciculus and amygdala-PFC tracts changed rapidly in early childhood and gradually from middle childhood to middle adolescence. While early changes were similar between sexes, females stopped exhibiting significant changes in left and right uncinate fasciculus FA 3.5–7 years before males. In contrast, females stopped the bulk of significant change in left uncinate fasciculus MD only 0.5 years before males and 0.8 years after males in right uncinate fasciculus MD. Our FA findings complement research reporting flatter profiles of uncinate fasciculus development in female versus male adolescents, suggesting earlier white matter maturation in females (Asato et al., 2010; Clayden et al., 2012; Geeraert et al., 2019; Wang et al., 2012). These findings are echoed by other work showing that FA and MD values peak in females before males (Chen et al., 2016). Our findings contrast with other studies that reported no sex differences in uncinate fasciculus trajectories, however, two of these studies used cross-sectional data and the other four longitudinal studies only examined 221–322 scans, compared to our 606 scan sessions (Krogsrud et al., 2016; Lebel et al., 2008, 2012; Lebel and Beaulieu, 2011; Muftuler et al., 2012; Simmonds et al., 2014). While both FA and MD are sensitive to changes in myelination, axon density, and fibre coherence (Lebel et al., 2019), some research suggests that FA is more closely related to changes in myelination (Chang et al., 2017), while MD is more closely related to changes in neurite density (Genc et al., 2017). Our FA findings may suggest greater sex differences in uncinate fasciculus myelination. Aligning with this, our supplementary analyses revealed that right uncinate fasciculus RD in males stopped significantly changing 5 years after females. While RD is speculated to be more sensitive to myelination than FA and AD (Goddings et al., 2021), previous work has also linked RD with axonal density differences (Klawiter et al., 2011). Additional investigations using more specific measures are needed to disentangle which biological factors drive the differences observed here. More protracted development in males was also seen in the left amygdala-PFC tract, where FA and MD changed for 4.5 and 1.3 years longer,

respectively, in males than in females. However, right amygdala-PFC tract FA and MD changed for 1.5 and 4.1 years longer, respectively, in females than in males. Lateralized sex differences in amygdala-PFC tract maturation may reflect asymmetrical sensitivities to sexually dimorphic factors like hormones or functional differences. For example, prior lesion work has shown that left hemisphere lesions in females cause greater impairments in emotional processing and impulsivity than right-sided lesions, while the opposite trend is seen in males (Sutterer et al., 2015; Tranel et al., 2005). In females, the right amygdala-PFC tract may be less involved in these behaviours than the left tract, resulting in more protracted development that supports other functions (Sutterer et al., 2015; Tranel et al., 2005). Further research is needed to understand the role of the amygdala-PFC tract in cognition and behaviour and the implications of sex differences.

Amygdala, PFC, and amygdala-PFC white matter mismatches may underlie sensation-seeking behaviour changes. Amygdala (Blair et al., 1999; Guyer et al., 2008; Phan et al., 2002; Schneider et al., 1997; Sergerie et al., 2008; Simpson et al., 2000; Moore et al., 2012) and PFC subregion (Bramson et al., 2020; Collette et al., 2001; Dong et al., 2022; Grecucci et al., 2013; Hampshire et al., 2010; Hartwigsen et al., 2019; Martín-Luengo et al., 2023; Martins et al., 2021; O'Doherty et al., 2001; Tyborowska et al., 2016; Volman et al., 2011) functional activation have been shown to influence sensation-seeking behaviours. Amygdala-PFC structural connectivity also modulates amygdala and PFC functional activation (Goetschius et al., 2019; Swartz et al., 2014) and sensation-seeking behaviours (Goldwaser et al., 2022; Ikuta et al., 2018; Rashidi et al., 2024). Sensation-seeking behaviours increase throughout childhood, peak in middle adolescence, and decline in adulthood (Haas et al., 2019; Harden and Tucker-Drob, 2011; Lydon-Staley and Geier, 2018; Romer et al., 2010; Shulman et al., 2015; Steinberg, 2008; Steinberg et al., 2018). Amygdala maturation in early to late childhood may promote early life sensation-seeking tendencies. Sensation-seeking behaviours may peak in adolescence because amygdala excitation continues without adult-like inhibitory signalling from slower to mature PFC regions. The prolonged maturation of amygdala-PFC white matter connections may contribute to an excitation-inhibition imbalance in adolescence by limiting communication between the amygdala and PFC. Sensation-seeking behaviours may decline and plateau in adulthood when the amygdala, PFC, and their connecting tracts have matured. Future work relating regional maturational timing patterns and sensation-seeking behaviour trajectories could clarify these relationships. It is also worth noting that while the amygdala is most commonly implicated in the DMH, other limbic structures may also play a role. Prior work has found that, on the participant level, the maturational timing of the nucleus accumbens and PFC was mismatched, but only in half of participants (Mills et al., 2014a). Nucleus accumbens and amygdala maturation was mismatched more regularly (Mills et al., 2014a). Exploring the DMH in other limbic structures and PFC subregions may reveal new relationships important for sensation-seeking behaviour.

Our findings may also help explain sex differences in sensation-seeking behaviours. The early plateauing of PFC volume in females suggests that PFC regions with amygdala connections mature earlier in females than in males. Early PFC maturation is associated with more adult-like functional activation capabilities (Kolk and Rakic, 2022). Throughout adolescence, the female PFC may produce more inhibitory signals during elevated emotion and reward processing than males, achieving an excitation-inhibition balance that results in early reductions in sensation-seeking behaviours (Shulman et al., 2015). Our findings indicate that amygdala-PFC white matter development ends earlier in females than in males. Increased myelination of structural connections has been associated with lower excitation/inhibition ratios and stronger functional connectivity in adults (Fotiadis et al., 2023). Earlier-developing females with more mature white matter microstructure may experience more effective amygdala-PFC communication than males, facilitating earlier reductions in sensation-seeking behaviours (Shulman et al., 2015).

Changing sex hormones may underlie sex differences in trajectories. Developing females and males experience surges in estradiol and testosterone, respectively, between 0 and 5 months (Andersson et al., 1998; Bidlingmaier et al., 1987). Infant MRI studies have reported faster growth in total brain volume in males than females (Villa et al., 2021) and sex differences in anterior cingulate gyrus and superior temporal gyrus volume trajectories (Khan et al., 2024). Early life hormone fluxes are one potential explanation for these infant sex differences (Khan et al., 2024; Villa et al., 2021). Females and males undergo another surge in sex hormones during puberty, between 8 and 14 years of age (Breehl and Caban, 2024). Pubertal amygdala and PFC volume and white matter tract FA and MD changes have been associated with estradiol and testosterone levels, illustrating a relationship between sex hormones and brain sexual dimorphism (Herting et al., 2014; Ho et al., 2020; Koolschijn et al., 2014; Menzies et al., 2014; Neufang et al., 2009; Vijayakumar et al., 2021). Estradiol and testosterone have also been negatively and positively, respectively, associated with self-reported sensation-seeking behaviours in 13–20 year olds (Harden et al., 2017). Further research is required to fully understand the neurobiological effects of sex hormone changes on brain development patterns and sensation-seeking behaviour.

Our sample is predominantly white, high-income, and highly educated. Because maternal education and household income have been associated with brain differences (Hair et al., 2022; Stephens et al., 2020; Zhu et al., 2023), our findings may not generalize to other sociodemographic contexts. Second, our sample was unevenly distributed across the age span, with more participants aged 2–13 years. Having fewer participants at older ages may result in less accurate representations of average population changes; larger samples are required to confirm. Lastly, we did not have measures of pubertal status or sensation-seeking behaviour, which would have strengthened the study. Future studies considering pubertal status and specific behaviours relating to the DMH will provide a more robust explanation of sex differences in developmental timing.

5. Conclusion

Our study found earlier amygdala development in childhood and later PFC development into adolescence. We saw that amygdala and PFC macrostructure and amygdala-PFC white matter microstructure maturational timing was mismatched. Our findings stand apart from previous DMH work by showing that the maturational timing discussed in the DMH is present in males and less apparent in females. Females undergo fewer and shorter periods of significant amygdala and PFC macrostructure change than males. Females also exhibited earlier amygdala-PFC white matter microstructure development than males. Together, these findings suggest that the amygdala-PFC neural system matures earlier in females than in males. Our large longitudinal study reveals nuances in how developmental mismatches manifest between grey and white matter and females and males, which may explain differences in the timing of behaviour development.

CRediT authorship contribution statement

Ghasoub Mohammad: Writing – review & editing, Methodology, Data curation. **Yeates Keith Owen:** Writing – review & editing, Methodology, Data curation. **Lebel Catherine:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Roeske Jamie:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Long Xiangyu:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Perdue Meaghan V:** Writing – review & editing, Methodology. **Long Madison:** Writing – review & editing, Methodology, Data curation. **Geeraert Bryce:** Writing – review & editing, Supervision,

Methodology, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2025.101568.

Data availability

A portion of the neuroimaging data used in this study are freely available through the Open Science Framework: https://osf.io/axz5r/, or the Canadian Open Neuroscience Platform: https://portal.conp.ca/dataset?id=projects/AdolescentBrainDevelopment. For more information, see Reynolds et al., (2020) and Geeraert et al., (2020). Other data are available upon reasonable request to the corresponding author.

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