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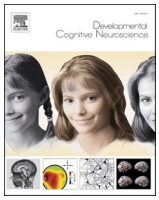

Linking brain maturation and puberty during early adolescence using longitudinal brain age prediction in the ABCD cohort

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ABSTRACT

The temporal characteristics of adolescent neurodevelopment are shaped by a complex interplay of genetic, biological, and environmental factors. Using a large longitudinal dataset of children aged 9–13 from the Adolescent Brain Cognitive Development (ABCD) study we tested the associations between pubertal status and brain maturation. Brain maturation was assessed using brain age prediction based on convolutional neural networks and minimally processed T1-weighted structural MRI data. Brain age prediction provided highly accurate and reliable estimates of individual age, with an overall mean absolute error of 0.7 and 1.4 years at the two timepoints respectively, and an intraclass correlation of 0.65. Linear mixed effects (LME) models accounting for age and sex showed that on average, a one unit increase in pubertal maturational level was associated with a 2.22 months higher brain age across time points ($\beta = 0.10$, $p < .001$). Moreover, annualized change in pubertal development was weakly related to the rate of change in brain age ($\beta = .047$, $p = 0.04$). These results demonstrate a link between sexual development and brain maturation in early adolescence, and provides a basis for further investigations of the complex sociobiological impacts of puberty on life outcomes.

1. Introduction

Brain development during adolescence is characterized by a highly coordinated sequence of both progressive (cell growth and myelination) and regressive (synaptic pruning) processes (Paus et al., 2008), observable as nonlinear trajectories of cortical thinning and white matter volume increase in relation to chronological age (Blakemore and Choudhury, 2006; Tamnes et al., 2010). The neurodevelopmental progress is most likely shaped by a complex interplay of genetic factors, changes in biological processes, and new environmental pressures (Fernandez-Cabello et al., 2022; Ferschmann et al., 2022). In parallel to brain development, adolescence is a period of drastic changes in physiological processes and body composition during puberty. Puberty refers to the reactivation of the hypothalamic pituitary gonadal axis that has remained dormant since early postnatal life, causing a steep increase in circulating gonadal steroids such as estradiol, progesterone, and testosterone (Campbell et al., 2009). The heightened levels of gonadal steroids primarily drive maturation of reproductive systems and secondary sex characteristics but puberty has also been linked to cortical (Vijayakumar et al., 2021) and subcortical gray matter (GM) (Goddings et al., 2014; Wierenga et al., 2018b), as well as white matter (WM) (Blakemore et al., 2010) brain maturation. Moreover, rodent studies have showed neurotrophic and neuroplastic effects of estrogen and testosterone (Filová et al., 2013; Hsu et al., 2003), and human longitudinal studies have linked endogenous estrogen exposure to beneficial effects on brain ageing (Schelbaum et al., 2021), supporting a direct effect of gonadal hormones on brain structure throughout the human lifespan in women (Galea et al., 2017; De Lange et al., 2020b). Given this

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evidence, puberty is a forefront candidate for biological processes shaping brain development during adolescence in addition to genetically programmed change.

The timing of puberty onset differs between the sexes with 1 year on average, such that females start their pubertal development between the ages 8 and 12, and males between ages 9 and 14 (Campbell et al., 2009). This one-year difference has been linked to the disproportion of depressive disorders, and depressive/internalizing symptoms, in young women (Pfeifer and Allen, 2021). Earlier onset of puberty has also been linked to positive effects such as higher academic achievements both in boys and girls, and may partly explain sex differences in educational achievement (Torvik et al., 2021). Although the mechanisms explaining sex differences in school performance are highly complex and multifaceted, it is conceivable that individual differences in brain maturation in early school years represent a relevant predictor for later life outcomes.

Related to their head start in puberty maturation, it is likely that females, at the group level, differ in the temporal characteristics of adolescent brain maturation compared to males. Attempts to elucidate relevant sex-differences in specific brain structures during adolescence and adulthood have yielded inconclusive and often contradicting findings (Lenroot and Giedd, 2010), which might be due to the narrow focus on predefined brain structures. In contrast, evidence points towards individually varying, mosaic compositions, of male/female like brain regions rather than a clear sexual dimorphism in overall brain structure (Joel and Fausto-Sterling, 2016). Thus, recent investigations of neural sex-differences have adopted a broader approach and moved towards multivariate integration of brain structures when distinguishing between male and female brain morphology (Brennan et al., 2021), multimodal investigations (Kaczkurkin et al., 2019), and investigating other characteristics of neurodevelopmental trajectories, such as sex differences in variability in brain structure (Wierenga et al., 2018a, 2019). As such, while the overall sex differences in brain morphology may be relatively small, the temporal characteristics of brain development during sensitive periods, such as puberty, may show additional relevant individual differences related to sexual development during adolescence.

In this study, in order to assess the overall relationship between pubertal development and brain maturation, and to investigate potential sex differences in brain maturational tempo, we linked pubertal development to early adolescents' brain age based on brain structural MRI. Pubertal development was assessed using parent-reported development of physical secondary sex characteristics (the Pubertal Developmental Scale (PDS); Petersen et al., 1988), and brain maturation was assessed using brain age prediction based on brain MRI. Brain age is a machine-learning based estimate of an individual's age based on their brain structural features. Supervised algorithms are trained to learn age-related patterns in brain structure from a large set of brain images with a wide age span, and can subsequently be applied to unseen datasets to predict age at the individual level. In adults, the difference between brain age and chronological age has been shown to represent a heritable trait (Cole et al., 2017; Kaufmann et al., 2019) and a range of clinically relevant characteristics and conditions have been associated with higher brain age (Tønnesen et al., 2020; Beck et al., 2022a, 2022b; De Lange et al., 2020a; Høgestøl et al., 2019). In children and adolescents, brain age has been interpreted as an indicator of overall level of brain maturation (Brown et al., 2012; Franke et al., 2012). Longitudinal assessments in adolescence have shown brain age to be heritable, higher in females than males (Brouwer et al., 2021), and linked to psychopathology and psychosocial functioning (Cropley et al., 2021; Drobinin et al., 2021). However, the clinical and functional correlates of brain age in adolescence have not been fully established.

In the current study, we calculated brain age using a recent deep learning approach based on convolutional neural networks (CNNs) in a large training set comprising minimally processed T1-weighted MRI data from > 50,000 individuals aged 5 to 93 years (Leonardsen et al., 2022). We applied the model to predict brain age in the Adolescent Brain Cognitive Development (ABCD) cohort, including 7459 baseline scans and 2384 scans from the first MRI follow-up two years later.

Based on current models and studies reviewed above, we expected cross-sectional and longitudinal associations between pubertal development and estimated brain age over and above chronological age. Specifically, independent of age, we hypothesized that 1) participants rated with more advanced puberty development would show higher brain age across time points. Next, we hypothesized that 2) higher rate of longitudinal pubertal development between time points would be associated with higher rate of brain age change. Furthermore, based on a recent report (Brouwer et al., 2021) we expected 3) higher brain age in females compared to males, likely explained by sex differences in pubertal development.

2. Methods

2.1. Sample characteristics

We used data from the ongoing longitudinal ABCD study, where more than 11,000 participants and their parents/guardians will be followed for ten years, with MRI data collection every second year (Garavan et al., 2018). Data used in the present study were downloaded in March 2022 as part of the ABCD Study Curated Annual Release 4.0 containing data from baseline up until the second-year visit (https://data-archive.nimh.nih.gov/abcd). To minimize confounding effects from complex family-related factors we included one participant per family for analysis. We excluded participants with known prenatal drug exposure, any serious medical, psychiatric, neurodevelopmental disorder and/or substance abuse, resulting in N = 7459 (3987 female) at timepoint 1, and N = 2384 (1239 female) at timepoint 2. The age distribution of the sample can be seen in Fig. 1.

2.2. Ethical approval

A centralized institutional review board approval of procedures was obtained from the University of California, San Diego. Written informed consent was obtained by parent or guardian, and assent from the participants, before partaking in the ABCD study.

The current study has been approved by the Regional Committees for Medical and Health Research Ethics South-East Norway.

2.3. MRI acquisition and processing

T1-weighted images were acquired with real time motion correction and imaging parameters harmonized for three 3 T scanner platforms (Siemens Prisma, General Electric (GE) 750 and Philips) (Casey et al., 2018) and minimally processed (skull stripping, reorientation, and normalization) as described in detail in Leonardsen et al. (2022).

2.4. Brain age calculations

The estimated brain age for each participant was calculated using a CNN trained and validated in minimally processed T1-weighted MRI data (n = 53,542 (27,715 females), 5–93 years) from 21 publicly available datasets (Leonardsen et al., 2022). The model architecture is a regression variant (SFCN-reg) of the PAC2019-winning SFCN model (Peng et al., 2021). The model was trained, optimized and validated in subsets of the data (n = 34,285 and 8455 respectively) and achieved a validation mean absolute error (MAE) of 2.51. More importantly, an MAE of 2.47 was observed in a subset of the original data containing previously unseen participants, and an MAE of 3.90 in an external dataset from unknown scanners indicates exceptional generalization properties.

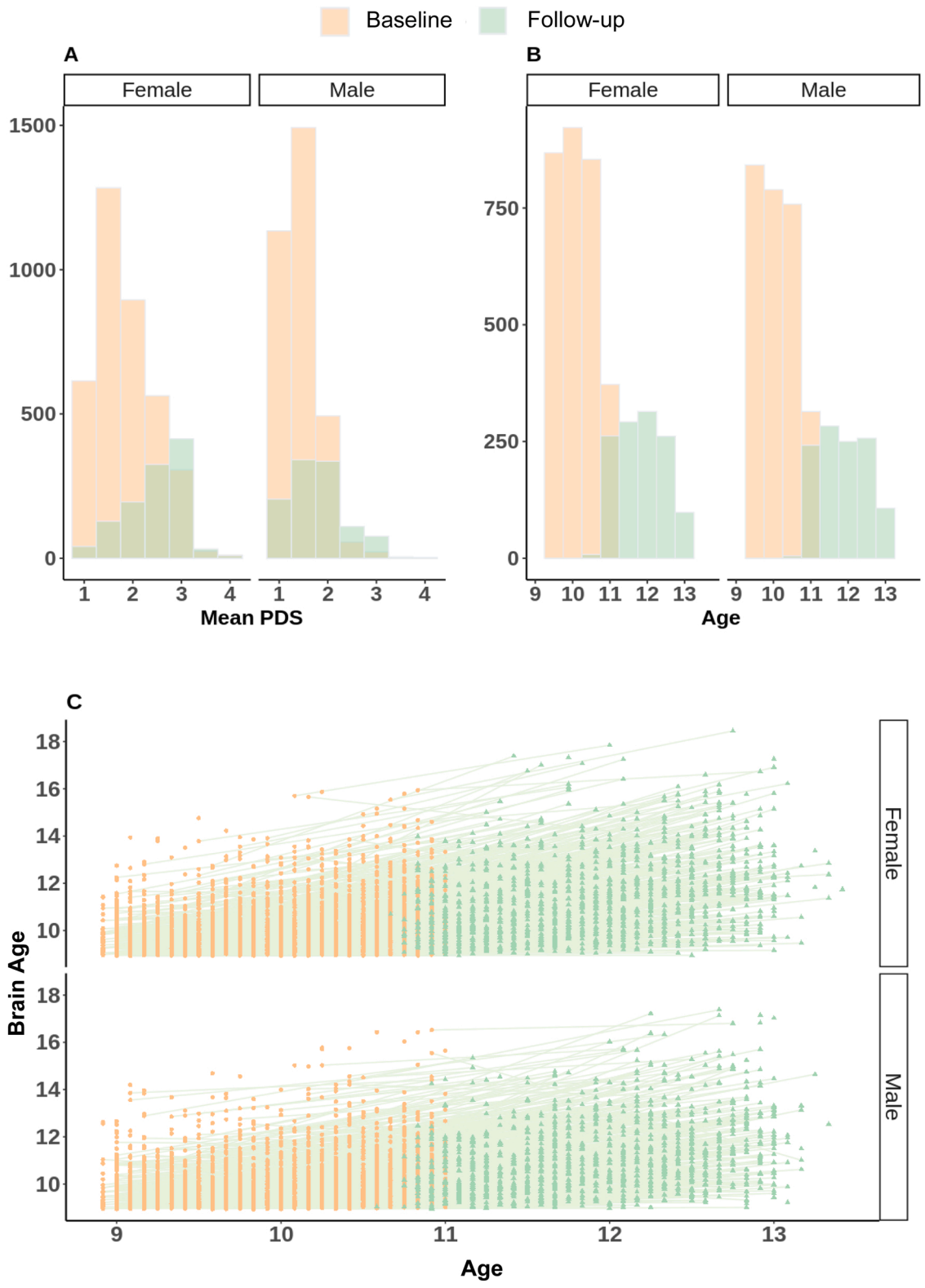

Fig. 1. A: Sample distribution of mean PDS at baseline and follow up. B: Age distribution at baseline and follow-up. C: The relationship between brain age and chronological age at baseline and follow up in the longitudinal sample, displayed by females and males separately.

2.5. Pubertal development assessment

Pubertal development was measured using PDS, a self or parent-rated questionnaire designed to mimic traditional Tanner staging assessment without the use of reference pictures (Petersen et al., 1988), in which puberty related development of physical secondary sex characteristics are ordinally rated. The questionnaire consists of seven items of which three are sex neutral, assessing skin changes, body hair changes, and growth in height. Two items are specific for females which are breast development and menarche (first menstruation), and two items are specific to males which are voice changes and facial hair growth. All items are rated on a scale of 1–4 (1: has not yet begun, 2: has

barely begun, 3: is definitely underway, and 4: seems complete). The exception is the menarche item, which is a binary response item. Both parent and child ratings are available. PDS has shown high inter-rater reliability between both parent and self-rated assessment to clinicians, and correlates highly with plasma levels of gonadal hormones (Carskadon and Acebo, 1993; Koopman-Verhoeff et al., 2020; Shirtcliff et al., 2009). For analysis, we used parent-rated development scores, which have generally been shown to have higher correspondence with trained clinician assessments than child-rated scores (Rasmussen et al., 2015). An average of the ratings across all PDS items was calculated for each subject and used in analyzes (mean PDS), which provided a summary measure of pubertal status across individual items. The sample distribution of mean PDS can be seen in Fig. 1.

2.6. Statistical analysis

All statistical analysis were implemented in R version 4.0.0 (R Core Team, 2021). We employed LME models of varying complexity to test our hypotheses, using the lmerTest package v. 3.1-3 (Kuznetsova et al., 2017). All coefficients were extracted in standardized format using sjPlot package (Lüdecke, 2021), which is a procedure equal to refitting the model on variables standardized by subtracting the mean of the variable and dividing by the standard deviation.

To assess our first hypothesis of an overall association between pubertal status and brain age, we tested two LMEs including estimated brain age as dependent variable and mean PDS scores as predictive variables: one only controlling for age, and one controlling for sex and age. The models used mean PDS, time point, age and sex as fixed effects, and scanner site and subject ID as random effects. These models were defined as:

Model 1) Brain age $= \alpha - \beta1 * \text{Mean PDS} + \beta2 * \text{timepoint} + \beta3 * \text{age} + b0i + b0ij + b1i$

Model 2) Brain age $= \alpha - \beta1 * \text{Mean PDS} + \beta2 * \text{sex} + \beta3 * \text{timepoint} + \beta4 * \text{age} + b0i + b0ij + b2$

where α denotes the intercept, β·s denoting the fixed effects slopes for sex, mean PDS scores, age, and change over timepoints 1 and 2, and $b0\acute{}s$ denoting random intercepts for subjects i and scanner j, and b1i denoting random slopes for mean PDS per participants.

Next, to assess our second hypothesis that the rate of longitudinal changes in pubertal development is associated with longitudinal changes in brain age, we tested a linear model of the association between annualized rate of change in predicted age and the annualized rate of change in mean PDS controlling for annualized rate of change in age. The annualized change rate was defined as the difference in values between timepoints divided by years between assessments. Using LMEs we also tested for interactions between mean PDS and timepoint with predicted age as outcome, to assess whether the change over time is dependent on the level of pubertal development. The model included sex, mean PDS, age, and timepoint as fixed factors, and subject ID and scanner site as random factors.

Model 3) Brain age $= \alpha - \beta1 * \text{timepoint} + \beta2 * \text{mean PDS} + \beta3 * \text{mean PDS} * \text{timepoint} + \beta4 * \text{age} + b0i + b0ij$

Where α denotes the intercept, β·s denoting the fixed effects slopes for sex, mean PDS scores, age, and change over timepoints 1 and 2, and $b\acute{}s$ denoting random intercepts for subjects i and scanner j.

Our third hypothesis of sex differences in brain age was tested in three models. One model assessed the main effect of sex, including only sex as predictor variable, controlling for age. The second model tested for sex differences in longitudinal change in brain age with an interaction term between sex and time. The third model tested for an interaction between sex and mean PDS to assess whether the males and females differ in their pubertal effects on brain maturation.

Model 4) Brain age $= \alpha - \beta1 * \text{sex} + \beta2 * \text{timepoint} + \beta3 * \text{age} + b0i + b0ij$

Model 5) Brain age $= \alpha - \beta1 * \text{sex} + \beta2 * \text{timepoint} + \beta3 * \text{sex} * \text{timepoint} + \beta3 * \text{age} + -b0i + b0ij$

Model 6) Brain age $= \alpha - \beta1 * \text{sex} + \beta2 * \text{timepoint} + \beta3 * \text{sex} * \text{mean PDS} + \beta3 * \text{age} + b0i + b0ij$

Where α denotes the intercept, β·s denoting the fixed effects slopes for sex, mean PDS scores, age, and change over timepoints 1 and 2, and b ś denoting random intercepts for subjects i and scanner j, and random slopes for mean PDS per participants.

All resulting p-values were corrected for multiple comparisons by false discovery rate using the p.adjust function in R (R Core Team, 2021).

3. Results

3.1. Descriptive statistics of pubertal development

Fig. 1 shows the distribution of mean PDS scores in males and females. LMEs revealed significantly higher mean PDS in females (mean = 2.09, SD = 0.65) compared to males (mean = 1.52, SD = 0.44, $t = 46.35$, $p < .001$) across timepoints. The models revealed a significant main effect of time ($t = 47.75$, $p < .001$), with higher mean PDS at follow-up (mean = 2.18, SD = 0.68) compared to baseline (mean = 1.67, SD = 0.53), and a significant interaction between time and sex, indicating that females had significantly higher change in mean PDS between the two assessments ($\beta = 0.33$ vs $\beta = 0.17$, $p < .001$).

3.2. Brain age prediction accuracy

Fig. 1C shows the distribution of brain age in females and males separately. Age was classified with a mean absolute error of 0.7 and 1.4 years at the two timepoints respectively, and an intraclass correlation of 0.65 between the two timepoints. A t-test comparing the difference scores between predicted age and chronological age of a small subset of subjects aged 11 from the two different timepoints (N = 78 from baseline, N = 97 from follow up) revealed no significant differences ($t = -0.669$, $p = 0.5$), indicating that the difference in MAE is not caused by any confounding factors affecting this measurement differently at the two timepoints.

3.3. The association between pubertal development and brain age

Table 1 and Fig. 2 summarize the fixed effects results from models 1 and 2, assessing main effects of pubertal status (hypothesis 1) on brain age. The results from model 2 show that, when including age and sex in the model, a one unit increase in pubertal maturational level (mean PDS) was associated with a higher brain age of 2.22 months ($\beta = 0.10$, $p < .001$), indicating a link between brain maturation and pubertal status across the two assessments. Further, a significant interaction effect between mean PDS and timepoint (Model 3, $p < .001$) indicated a stronger association between puberty and brain age at follow-up than baseline. The linear model analysis revealed a small association between annualized rate of change in PDS scores and annualized rate of change in predicted age when controlling for annualized rate of change in age (β(standardized) = .047, $p = 0.04$).

3.4. Sex differences in brain age

Table 1 and Figs. 2 and 3 summarize the fixed effects from models assessing sex differences in brain age (model 3 and 4). When including mean PDS in the models, females had a significantly lower brain age of almost one month across timepoints compared to males (Model 2,

Table 1
Results from linear mixed effects models on brain age, reporting standardized coefficients and FDR corrected p-values.

Term	beta	SE	CILL	CIUL	Statistic	p
Model 1						
Age	0.38	0.02	0.35	0.41	23.43	< .001
Mean PDS	0.08	0.01	0.06	0.1	7.52	< .001
Timepoint	0.08	0.01	0.05	0.11	5.42	< .001
Model 2						
Age	0.37	0.02	0.34	0.41	22.91	< .001
Mean PDS	0.1	0.01	0.07	0.12	8.08	< .001
Sex(female)	-0.06	0.02	-0.01	-0.02	-3.03	0.003
Timepoint	0.08	0.01	0.05	0.11	5.4	< .001
Model 3						
Age	0.39	0.02	0.36	0.43	23.79	< .001
Mean PDS	0.07	0.01	0.05	0.09	6.91	< 0.01
Timepoint	0.05	0.01	0.02	0.08	3.24	0.002
M.PDS * Timepoint	0.07	0.01	0.05	0.08	9.52	< .001
Model 4						
Age	0.42	0.02	0.39	0.45	25.67	< .001
Sex(female)	0.03	0.02	-0.01	0.06	1.42	0.163
Timepoint	0.08	0.01	0.05	0.1	5.05	< .001
Model 5						
Age	0.42	0.02	0.39	0.45	25.68	< .001
Sex(female)	0.03	0.02	0	0.07	1.75	0.089
Timepoint	0.04	0.02	0.01	0.07	2.55	0.012
Sex * Timepoint	0.06	0.01	0.04	0.09	4.63	< .001
Model 6						
Age	0.39	0.02	0.35	0.42	23.24	< .001
Sex(female)	-0.07	0.02	-0.11	-0.02	-3.09	0.003
Mean PDS	0.12	0.02	0.08	0.15	6.28	< .001
Timepoint	0.07	0.01	0.04	0.1	4.53	< .001
Sex * M.PDS	-0.03	0.02	-0.07	0.02	-1.22	0.222

$\beta = -0.06$, $p < .001$). When omitting mean PDS from the model, the sex differences in brain age were not significant (Model 4, $\beta = 0.02$, $p = .2$).

A significant interaction effect between sex and timepoint was observed (model 5, $p < .001$), with follow up analysis indicating larger increase in brain age over time in females compared to males ($\beta = 0.14$, vs $\beta = 0.08$).

Sex-specific models revealed a significant relationship between pubertal development and brain age in females ($\beta = 0.07$, $p < .001$) and males ($\beta = 0.13$, $p < .001$). The strengths of the associations were not significantly different, as indicated by a non-significant interaction term (Model 6, sex * mean PDS, $p = .22$).

4. Discussion

The age of pubertal onset has been linked to several real-life outcomes, including educational achievements and psychopathology. Puberty-related influence on brain maturation could represent a relevant explanatory or mediating factor, and could also provide a window to the study of sex differences in brain and behavior. In the current study longitudinal brain age prediction during a sensitive period of early adolescence revealed a positive association between parent-rated pubertal development and brain age, indicating a relationship between pubertal development and brain maturation over and beyond chronological age. Compared to males, females exhibited a more advanced and a faster pace of pubertal development and also a higher rate of changes in brain age between time points. When accounting for sex differences in pubertal development, females exhibited an overall slightly lower brain age than their male peers across timepoints, which was not evident

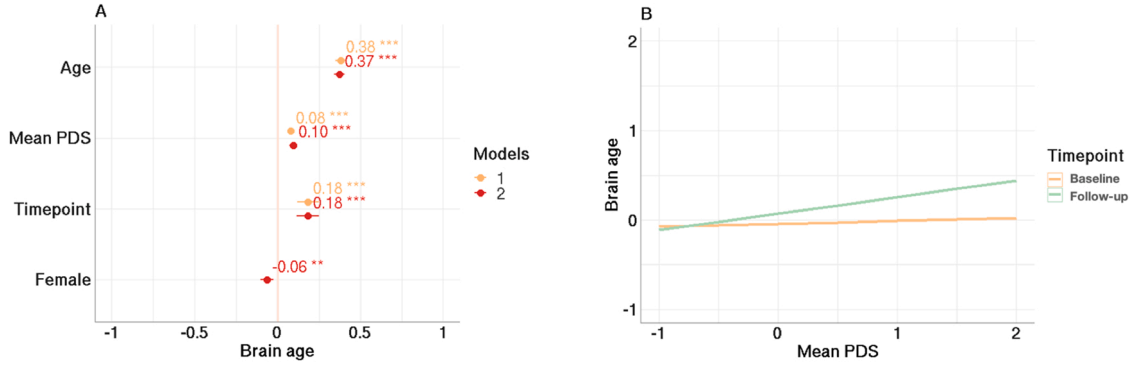

Fig. 2. Associations between puberty and brain age. A: Standardized parameter estimates reflecting main effects obtained from model 1 and 2, with and without sex included in the model. The error bars reflect the 95 % confidence interval. B: The interaction between mean PDS and timepoint, indicating a moderating effect of puberty on brain age, in particular at follow-up.

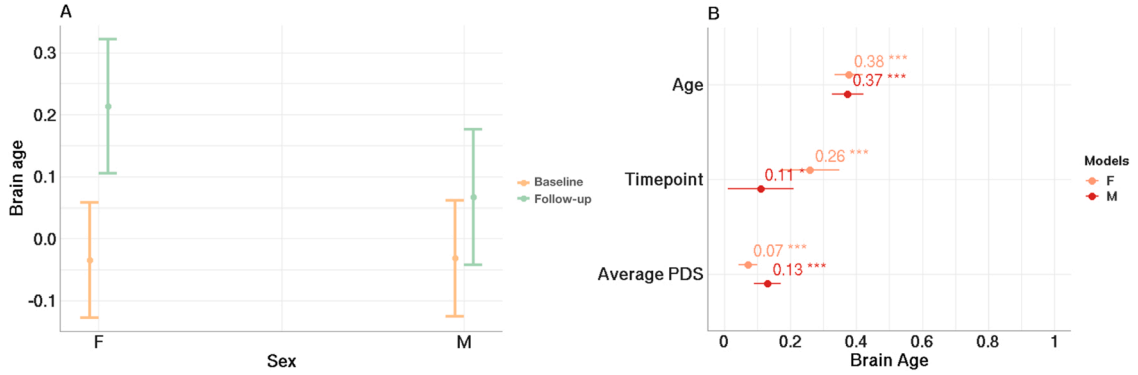

Fig. 3. Sex specific effects of puberty and longitudinal development of brain age. A: Interaction between sex and time from model 5, showing larger longitudinal changes in brain age in females compared to males while controlling for mean PDS. B: The relationship between mean PDS, timepoint, and brain age within females and males, respectively (interaction not significant).

when omitting pubertal status from the models.

4.1. Pubertal development and brain age

The results from models assessing main effects of PDS on brain age across timepoints showed that a one unit increase in mean PDS score was related to a higher brain age of 2.22 months, when controlling for sex and age. This supports our first hypothesis of a contribution of pubertal development to overall brain maturation, in line with previous research linking pubertal development to morphological changes in brain structure (Goddings et al., 2014; Vijayakumar et al., 2021; Wierenga et al., 2018a, 2018b). The annualized change in pubertal developmental scale was weakly related with the annualized change in brain age, indicating that the rate of change in pubertal development over time is partly reflected in the rate of change in brain maturation. Pubertal development also significantly interacted with time in relation to brain age, indicating that changes in brain age over time depends on pubertal stage and development. The effect sizes were moderate and comparable to previous studies using other neuroimaging based outcomes to study the associations between brain structure and puberty (Vijayakumar et al., 2021). Brain development during adolescence is likely shaped by an interaction of genetically programmed age-related changes, biological processes, and fluctuating environmental pressures (Fernandez-Cabello et al., 2022; Ferschmann et al., 2022). Combined with previous findings, our study shows that the effects of puberty are non-negligible and should be considered an influencing factor when studying adolescent brain development.

4.2. Sex differences in adolescence brain age

The developmental processes shaping adolescent and adult sex differences in brain and behavior comprise a combination of hard-wired biological processes and complex sociocultural and environmental influences, and their dynamic interactions. Adolescence is a period when sex-differences in school performance and other life outcomes emerge, for which pubertal development has been proposed among the candidate driving mechanisms (Torvik et al., 2021; Pfeifer and Allen, 2021). Due to the surge in gonadal hormones, and their known neuroplastic effects (Hsu et al., 2003; Filová et al., 2013; Schelbaum et al., 2021; Galea et al., 2017; De Lange et al., 2020b) sex-differentiation of brain structure and function is believed to be largely shaped during puberty. However, there appear to be no obvious general dichotomization between a female and male brain (Joel and Fausto-Sterling, 2016; Lenroot and Giedd, 2010) that could explain the psychological differences. Research instead show that females and males differ in other aspect of neurobiology such as overall variance in brain morphology (Wierenga et al., 2018a, 2018b, 2019) and the impact of gonadal hormones on specific brain structures (Bramen et al., 2011, 2012). As females on average have an earlier onset of puberty than males (Campbell et al., 2009), we theorized that the differences in maturational tempo could be reflected in maturational tempo of the brain. Thus, we hypothesized that the earlier maturation would be reflected in an overall higher brain age in females.

We found no support for our hypothesis of an overall higher brain age in females. Instead, LMEs including pubertal status and time effects revealed overall lower brain age among female compared to male participants across time points, albeit with small effect size. Moreover, sex specific LMEs showed that females had a lower association between pubertal status and brain age compared to males, although this difference was not significant. Females did, however, show a stronger relationship between pubertal maturation and brain age at follow up, when they were also significantly more pubertally developed than males.

Our finding of an overall lower brain age in female compared to male participants when controlling for pubertal status contradicted our initial hypothesis, and contrasts the findings from a recent study including 330 youth aged 12–17 years reporting that female participants had a higher brain age than their male peers (Brouwer et al., 2021). As our analysis revealed no significant sex differences when omitting pubertal status from the model, the discrepancies with the previous report might be partly due to sex differences in pubertal maturation status and the different age ranges and level of maturation in the two samples, and could indicate that pubertal status drives sex-differences observed in previous studies. However, these effects should be interpreted with caution as the estimates might be subject to influence from the different variability in mean PDS scores between sexes.

Moreover, both cross-sectional and longitudinal sex-effects were relatively small compared to overall pubertal and age estimations. Although, the possibility to estimate small effects is generally a benefit in large sample sizes, the small effect size calls into question the relevance of these effects in a broader context. Small sex-difference in brain maturation might have a small relevance in relation to the larger sex-differences in psychological traits. However, the young age in our sample, and consequently their early status of pubertal development, could also indicate that these effects are early signs of later observable sex-differences in brain maturational tempo. Further studies assessing a wider age range and a higher number of assessments across a larger time interval are warranted to test this hypothesis. Subsequent follow-up assessments of the ABCD cohort will be able to pursue this hypothesis further, and may further characterize the involvement of pubertal development in the brain developmental processes laying the foundation of sex differences in complex traits and behaviors in adulthood.

Although some sex-differences in brain structure are well replicated, such as a larger total brain volume in males, there are many inconsistent findings regarding sex-differences in brain morphology at large (Lenroot and Giedd, 2010; Ritchie et al., 2018). As adolescence is a period during which sex differences in psychological function emerge (Torvik et al., 2021; Pfeifer and Allen, 2021), further research on sex differences in neurodevelopmental trajectories are needed. Our findings of sex differences in brain age change are relatively small compared to the observed relationships with age and pubertal development. However, they may point to relevant sex differences in the tempo of brain maturational processes that should be considered when studying the emergence of human brain sex differences during adolescence.

4.3. Strengths and limitations

Key strengths of our study include the large number of subjects and the longitudinal aspect of our data, enabling analysis of changes in brain age over a period of two years and sufficient power to reduce uncertainty of the estimates and detect relatively small effects.

The narrow age range in our sample may have provided more power to disentangle the effects of age and puberty on brain maturation. Age and pubertal development are highly correlated, and it has been suggested that studying a sample with a shorter age-range could disentangle the brain maturation attributable to age and pubertal development variability (Goddings et al., 2019). However, due to the young age of the sample we were not able to capture the complete developmental trajectory during the full course of puberty, as youths have just experienced the onset of puberty at this age. Thus, our results can be best described as capturing the effects of early pubertal development. Moreover, assuming that gonadal steroids is one of the biological factors driving the pubertal impact on brain development, there may be a time difference in their effect on neural properties compared to physiology, such that effect on brain properties are more detectable later in development. The young age and overall early pubertal status in our sample thus prohibits any analysis of potential temporal delay between the onset of puberty and its effect on brain maturation. Another challenge to the interpretation of the observed relationships between pubertal development and brain maturation is the possible confounding effects of socioeconomic factors such as poverty, air pollution and parental education and their complex interactions with genetic factors, both through direct and indirect effects (Bleil et al., 2017; Styne, 2004).

Relatedly, future studies should test to which degree lifestyle and health-related behaviors such as physical activity, nutrition and obesity mediate the current association between puberty and adolescent brain development (Beck et al., 2022a; Bleil et al., 2017; Styne, 2004).

Brain age was derived from a deep learning model without predefined regions of interests, providing an anatomically unbiased estimate of brain age. This might be advantageous in a young age sample as the neurodevelopmental trajectories during adolescence is heterogeneous and non-linear across individuals and brain regions (Østby et al., 2009). The training and validation of the model was performed in a dataset with an age range spanning the full lifespan, while the analyzes were performed in data spanning a narrow age-range during early adolescence. The differences in MAE accompanied by a difference in mean error of 0.6 years between the two timepoints. As there was no difference between the predicted age and chronological age from subjects in the same age span but from different timepoints, we believe the difference in MAE between timepoints to be caused by local age bias in the DL model used. The general age bias was controlled for in LME models, and is not necessarily a problem. The lower brain age in females, however, should be interpreted with caution as it could indicate that the validation procedure might not have been sensitive enough to pick up non-linear, local sex-specific age bias in the given age range. Although no major imbalance of sex-distributions was obvious in the training and validation sets, future studies using similar methods need to pay extra attention to balancing training and test sets in this age group when replicating these results.

Further, while the brain age model provided highly accurate estimates based on anatomically unbiased information, it was only informed by the signal embedded in the T1-weighted MRI data. It is possible that a multimodal approach integrating different imaging modalities could have provided brain age estimates with varying levels of sensitivity and specificity (Rokicki et al., 2021), which could offer the opportunity to triangulate different biological processes related to puberty and brain maturation. Further studies using a wider range of the rich neuroimaging data available in the ABCD study may be able to test this hypothesis.

A final limitation to our methods is the subjective nature of the pubertal assessment. Although parent rated PDS has shown high inter-rater reliability compared to clinician rated Tanner staging (Koopman-Verhoeff, 2020; Carskadon and Acebo, 1993), there might be variability in the parents'/caregivers' awareness of their children's pubertal development that could not be controlled for. In sum, future studies will benefit from a wider age-span of subjects (and consequently more developed in puberty) when investigating the effects of puberty on brain maturation, as well as from objective assessment of puberty via blood plasma or saliva assessment of sex-steroids. Long-term follow-up assessments are required to assess the long-term real-life impact of individual differences in the onset and pace of puberty and its associations with brain maturation.

Taken together, this study suggests that pubertal development mediates overall brain maturation during adolescence. Although the sex differences in brain age were relatively small, females presented with more advanced and higher rates of changes in their pubertal development and also exhibited larger changes in brain age between baseline and follow up. Thus, our results indicate a link between the temporal characteristics of pubertal and brain development that may be provide a relevant window into the neurodevelopmental and neuroendocrinological origins of sex-differences in relation to mental health and other life outcomes.

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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