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Running Head: Puberty, Adolescent Neurodevelopment, and Inhibitory Control

Puberty contributes to adolescent development of fronto-striatal functional connectivity supporting inhibitory control

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Abstract

Adolescence is defined by puberty and represents a neurobiological period characterized by enhanced neuroplasticity facilitating cognitive improvements. Fronto-striatal systems undergo important specialization throughout adolescence, supporting developmental changes in cognition and motivated behaviors. Though studies have characterized age-related changes, the extent to which puberty influences maturation of fronto-striatal networks is less known, limiting our understanding of unique adolescent processes. Here, we combine two longitudinal datasets to characterize the role of puberty in the development of fronto-striatal resting-state functional connectivity (rsFC) and its relationship to inhibitory control in 110 10-18-year-olds. Not surprisingly, age-effects evident with older age ranges were not present in this sample. After controlling for age effects still possibly present, puberty was associated uniquely with late increases rsFC of nucleus accumbens (NAcc) and dorsolateral prefrontal cortex (dlPFC) in both males and females and early puberty increases with ventrolateral PFC (vlPFC) in females. Additionally, greater dlPFC – NAcc rsFC was associated with worse inhibitory control performance in early puberty while vlPFC – NAcc was associated with response latency. Taken together, our findings suggest that mid-late puberty is a crucial period for lateral PFC – NAcc circuitry maturation, which may contribute to critical aspects of developmental improvements in inhibitory control function into adulthood.

Keywords: adolescence; puberty; resting-state functional connectivity; inhibitory control

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Introduction

Puberty demarcates the start of adolescence, the transitionary period of development to adulthood characterized by widespread biological, cognitive, and behavioral maturation. By the end of the adolescent period, individuals are better able to reliably engage brain circuitry that supports goal-directed cognitive processes (e.g., response inhibition) (Ordaz et al., 2013). In particular, inhibitory control continues to improve into the second decade of life as the percent of correct inhibitory responses increases and the latency to initiate a correct response decreases (Luna et al., 2004; Ordaz et al., 2017). Central to the development of these cognitive processes are maturational changes within fronto-striatal networks, comprised of prefrontal cortical (PFC) regions and striatal structures, such as the nucleus accumbens (NAcc), and their functional connectivity (Parr et al., 2021). What remains unclear, however, is the extent to which pubertal maturation contributes to the development of fronto-striatal circuitry to the adolescent transition to adult-level cognitive control beyond well-characterized age-related effects (Bos et al., 2012; Anna C. K. van Duijvenvoorde et al., 2019; Fareri et al., 2015; Harsay et al., 2011; Parr et al., 2021). Studies in adolescents have largely relied on chronological age as the developmental variable of interest; however, investigating the effects of puberty (independent of age) represents an understudied area that is crucial to developing a more comprehensive understanding of the distinct mechanisms underlying adolescent neurodevelopment. This is due, in part, to observations suggesting that puberty has high inter-individual variability (Short and Rosenthal, 2008), is associated with psychopathological risks (Kuhn et al., 2010; Pfeifer and Allen, 2021), and posits specific biological mechanisms underlying both the developmental improvements in behavior as well as increased risk for the emergence of psychopathology (e.g., mood disorders, substance use disorders, psychosis) (Paus et al., 2008) as well as sex differences in rates of mood and anxiety disorders during this period (Angold and Worthman, 1993). Pubertal maturation is strongly associated with psychopathological risk (Ho et al., 2021; Ladouceur et al., 2012; Mendle et al., 2010), particularly in girls (Oldehinkel et al., 2010), and some work suggests that puberty may better predict adolescent psychopathologies, such as substance use and depressive disorders, over and above age-related risks (Kuhn et al., 2010; Pfeifer and Allen, 2021). As such, investigating the unique contributions of puberty to neurodevelopment beyond age-related effects may provide a set of biological mechanisms that can clarify inter-individual differences in cognitive maturation across typical and atypical adolescent development.

Puberty—via its hormonal effects—impacts both physical maturation, resulting in the development of secondary sexual characteristics, and reproductive behaviors (Sisk and Foster, 2004). Importantly, it also contributes to cognitive changes, including in attentional and motivational processes (Hebbard et al., 2003; Romeo and Sisk, 2001; Sato et al., 2008). Animal studies have demonstrated that pubertal hormones are necessary for the formation of adult-like behavior. Interference with gonadal steroids during adolescence, via castration or pharmacological blockage, for example, produces deficits in adult-typical behaviors, such as social interactions, even if hormones are later restored to typical levels in adulthood (Primus and Kellogg, 1990, 1989). Several studies have proposed that pubertal contributions to adolescent neurodevelopment occur, in part, via the influence of sex hormones on estrogen and estradiol receptors in the brain (Ho et al., 2020; Poon et al., 2019), which may mediate experience-dependent plasticity, allowing large-scale refinement and specialization of cognitive-affective networks, several of which may be especially sensitive to the stimulating and novel environments adolescents explore and exploit (Murty et al., 2016). These findings suggest that adolescence may reflect a critical period during

which the effects of hormones on relevant neural circuitry determine cognitive and behavioral development (Larsen and Luna, 2018).

Central to facilitating goal-directed behaviors is the NAcc, which is innervated by dense dopaminergic projections originating in the ventral tegmental area (VTA) (Voorn et al., 1986). The NAcc undergoes substantial structural and functional maturation during adolescence (Larsen and Luna, 2014; Walhovd et al., 2014), and several human neuroimaging studies have observed increased NAcc activation during adolescence, potentially contributing to developmental peaks in reward-driven and risk-taking behaviors (Braams et al., 2015; Ernst et al., 2005; Galvan et al., 2006; Geier et al., 2009; Geier and Luna, 2012; Padmanabhan et al., 2011; Silverman et al., 2015). Further contributing to enhanced reward sensitivity, studies have shown heightened VTA – NAcc (Murty et al., 2018) and ventromedial prefrontal cortex (vmPFC) – NAcc (Anna C K van Duijvenvoorde et al., 2019; Fareri et al., 2015; Parr et al., 2021) functional connectivity in adolescence during rewarded states that decreases into adulthood, supporting developmental decreases in risk-taking behavior (Parr et al., 2021). Importantly, salivary testosterone has been shown to mediate age-related changes in resting-state functional connectivity (rsFC) between the NAcc and medial PFC (Fareri et al., 2015), suggesting that NAcc circuitry bridging midbrain dopamine systems and prefrontal decision-making regions may be particularly sensitive to pubertal maturational processes.

The present study seeks to bridge several of gaps in the field in terms of understanding the role of puberty in fronto-striatal contributions to cognitive development. Using data from two longitudinal adolescent samples, we investigated the effects of pubertal maturation on fronto-striatal rsFC after accounting for age-related effects. Based on previous findings, we hypothesized that pubertal maturation would be differentially associated with rsFC between medial frontal areas (e.g., ventromedial PFC (vmPFC) and anterior cingulate cortex (ACC) subregions) and the NAcc—which we expect to decrease with pubertal maturation, given past findings of dopamine-mediated age-related decreases in reward state fronto-striatal functional connectivity (Parr et al., 2021) and its role in developmental changes in reward sensitivity (Blakemore, 2008; Crone, 2014; Duijvenvoorde et al., 2015; Jones et al., 2014). In contrast, we expect lateral frontal areas (e.g., dorsolateral and ventrolateral PFC (dlPFC, vlPFC)) rsFC with the NAcc to increase with pubertal maturation, given their role in improvements related to executive functions, such as cognitive control (MacDonald et al., 2000), response inhibition (Luna et al., 2001), and age-related decreases in risk-taking behaviors (Qu et al., 2015). Furthermore, we expect that female participants will exhibit earlier puberty-related fronto-striatal functional maturation relative to male participants, given their relative timing of pubertal development. Finally, given evidence implicating these networks in developmental changes in cognition (Morein-Zamir and Robbins, 2014) through adolescence, we will explore the association between puberty-related maturation within fronto-striatal networks and inhibitory control performance as measured by the antisaccade task. Taken together, this work will contribute to deepening our understanding of the role of puberty as it relates to cognitive improvements observed during the adolescent period.

Methods

2.1. Participants

Participants were drawn from two large, longitudinal neuroimaging studies which have been previously reported (Calabro et al., 2019; Parr et al., 2022, 2021). For our primary analyses, we restricted our sample to participants ages 10-18 within these samples, who were assessed for pubertal stage (assessment described below) and had assessments indicating they had started pubertal maturation, resulting in a sample of 110 adolescents (52 females) with 1-3 longitudinal visits each at approximately 12-18 month intervals, for a total of 266 scan sessions. One of the cohorts was also examined in a separate paper looking at puberty effects on wide ranging connectivity and inhibitory performance (Ravindranath et al., 2022, submitted to this issue). Participants were recruited from the community and screened for the absence of neurological or psychiatric problems including loss of consciousness, self or first-degree relatives with major psychiatric illness, and MRI scanning contraindications (e.g., claustrophobia, metal in body, pregnancy). Participants under the age of 18 provided assent and parents of participants provided informed consent. Experimental procedures were approved by the University of Pittsburgh Institutional Review Board and complied with the Declaration of Helsinki.

To contextualize findings across adolescence and into early adulthood, we additionally report data from an extended sample, which includes those described above, in the Supplement (**Figure S1**). This larger sample consisted of 286 participants (152 females, ages 8 - 34) who completed up to 13 longitudinal visits for a total of 799 sessions.

2.2. Puberty assessment

Pubertal assessments were collected in participants ages 18 and under using the Petersen Pubertal Development Scale (PDS) (Petersen et al., 1988), a self-report measure of physical development. The PDS is comprised of five questions about physical development, differing for males and females, with possible item scores ranging from 1 (development has not yet begun) to 4 (development appears complete), and includes several additional (secondary) sexual characteristic questions not captured by Tanner staging (e.g., skin and hair changes). Composite scores were transformed to a 5-point scale for comparison to Tanner scale stages. Given our interest in the role of pubertal maturation, participants were included in the pubertal analyses if their transformed-PDS score indicated pubertal development was already underway (transformed-PDS score ≥ 2). See **Figure 1** for participant age (A) and puberty distributions in the sample (B).

2.3 Eye tracking data acquisition

Eye tracking data were captured using an eye-tracking system (M5000, Applied Science Laboratories) with a sampling rate of 60 Hz. Real-time monitoring enabled identification of head movement or inattention to the task, in which case, experimenters redirected subjects following the run. A 9-point calibration routine was performed at the beginning of each session. Responses were scored with a custom scoring script written in R (see (Ravindranath et al., 2020) for details).

2.4 Antisaccade task

Participants completed a total of 48 antisaccade (AS) trials at each visit, performed outside of the scanner (previously described in (Ordaz et al., 2013) and (Ravindranath et al., 2020)). Each AS trial began with a red fixation cross presented at the center of a black screen for 500-6000 ms followed by a 200 ms black screen. Next, a yellow "cue" dot appeared pseudo-randomly (evenly distributed between four positions on the horizonal meridian at 2%, 33%, 66%, or 98% of the screen width) on the screen for 1000 ms along the horizontal axis in the center of the screen followed, by a 20 ms response period (black screen) during which participants were instructed to direct their gaze away from the location of the yellow cue and instead, look at the mirror location on the screen. See **Figure 2** for a schematic of the antisaccade task.

AS responses were considered "correct" if the first eye movement during the saccade epoch had a velocity ≥ 30°/second toward the mirror location of the yellow cue and extended beyond a 2.5°/visual angle from central fixation. A trial was considered an error if the first saccade in the response epoch was directed toward the peripheral stimulus and extended beyond 2.5° central fixation window. Trials were considered error-corrected if an error was followed by a correct response. Express saccades, which are too rapid to engage cognitive systems, were excluded and defined as a saccade starting within the first 4 samples (60Hz) after trial onset. For the current study, we focused our analyses on correct antisaccade trials. Our two inhibitory control variables of interest were antisaccade "performance" (number of correct / total usable trials) and mean latency—the time from when the stimulus appeared to saccade onset (in ms)—on correct trials.

2.5. MR data acquisition

MMR dataset

MR data were acquired on a 3T Siemens Biograph molecular Magnetic Resonance (mMR) PET/MRI scanner. Structural images were acquired using a T1 weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR, 2300 ms; echo time (TE), 2.98 ms; flip angle, 9°; inversion time (TI), 900 ms, voxel size, 1.0 x 1.0 x 1.0 mm). Functional images were acquired using blood oxygen level dependent (BOLD) signal from an echoplanar sequence (TR, 1500 ms; flip angle, 50°; voxel size, 2.3 x 2.3 x 2.3 mm in-plane resolution) with contiguous 2.3mm – thick slices aligned to maximally cover the cortex and basal ganglia. Two 8-min sessions of fixation resting-state fMRI (rsfMRI) data were collected prior to and following a task-based fMRI sequence, respectively.

CogLong dataset

MR data were acquired on a Siemens 3T MAGNETOM Allegra. Structural images were acquired using a T1 weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR, 1570 ms; TE, 3.04 ms; flip angle, 8°; TI, 800 ms, voxel size, 0.78125 x 0.78125 x 1.0 mm). Functional images were acquired using BOLD signal from an echoplanar sequence (TR, 1500 ms; TE, 25 ms; flip angle, 70°; voxel size, 3.125 x 3.125 mm in-plane resolution) with contiguous 4-mm-thick slices aligned to the subject's anterior-posterior commissure plane.

rsfMRI data were extracted from the OFF periods of a mixed block-event-related design (Ordaz et al., 2013) based on a previously reported method (Fair et al., 2007). Briefly, during ON periods, participants completed either a pro- or anti-saccade task. Functional images were

extracted from the OFF periods, excluding the 15 s following the preceding ON period. Across the four runs, 6:48 min of rsfMRI data were produced. See (Calabro et al., 2019) for additional details.

2.6. MR data preprocessing

Structural MRI data were preprocessed to extract the brain from the skull and warped to the MNI standard using both linear (FLIRT) and non-linear (FNIRT) transformations. rsfMRI data were preprocessed using a pipeline that minimized the effects of head motion (Hallquist et al., 2013) including 4D slice-timing and head motion correction, skull stripping, intensity thresholding, wavelet despiking (Patel et al., 2014), coregistration to the structural image and nonlinear warping to MNI space, local spatial smoothing with a 5mm Gaussian kernel based on the SUSAN algorithm, intensity normalization, and nuisance regression based on head motion (6° of translation/rotation and their first derivative) and non-gray matter signal (white matter and CSF and their first derivative). Bandpass filtering between .009 and .08 Hz was done simultaneously with nuisance regression. Frame-wise motion estimates were computed for resting-state data. Functional volumes containing frame-wise displacement (FD) > 0.3 mm were excluded from analyses (Siegel et al., 2013). Participants with more than 40% of TRs censored were excluded altogether from rsfMRI analyses. Neuroimaging analyses were performed in AFNI (Cox, 1996).

2.7. Region of interest (ROI) selection

We used a region of interest (ROI) approach to investigate fronto-striatal connectivity between hypothesis-driven, *a priori* ROIs. In the striatum, we focused analyses on the NAcc, a prominent node of reward processing networks which has been previously implicated in the development of goal-directed behavior (Mannella et al., 2013), including performance of the antisaccade (Murty et al., 2018). Left and right NAcc were defined using the Harvard-Oxford subcortical atlas (Jenkinson et al., 2012). We assessed connectivity between the NAcc and prefrontal regions known to support reward learning and cognitive processing, processes that undergo significant maturation through adolescence, including dlPFC, vlPFC, anterior vmPFC, and subgenual, rostral, and ventral ACC (sgACC, rACC, vACC, respectively). Bilateral vmPFC subregions, which included the anterior vmPFC, sgACC, rACC, and vACC, were defined based on the Mackey and Petrides atlas (Mackey and Petrides, 2014). We excluded orbitofrontal cortex (OFC) ROIs from analyses due to relatively lower temporal signal-to-noise ratios (tSNRs) for these PFC subregions relative to the others. The dlPFC ROI was defined using the MNI Glasser Human Connectome Project atlas (Glasser et al., 2016). The vlPFC ROI was defined using the Brainnetome atlas (Fan et al., 2016). Voxels were required to have at least a 50% or greater probability of being gray matter in the MNI-152-09c template to be included in each ROI. As such, the final PFC ROIs included the anterior vmPFC (area 14m), sgACC (area 25), rACC (area 32), vACC (area 24), dlPFC (areas 8, 9, and 46), and vlPFC (areas 44, 45, and 47). See **Figure 3** for a representation of these ROIs.

2.8 ROI functional connectivity analyses

Time series were extracted from each participant's preprocessed resting-state functional images by taking the first principal component across all voxels within each ROI (Zhou et al., 2009). Pearson correlation coefficients were then computed between ROI seeds and normalized

using Fisher's Z transformation. rsfMRI connectivity data were harmonized between the two longitudinal studies using NeuroComBat (*neuroCombat* in R, R Core Team, 2020) to account for scanner acquisition differences while retaining biological variability of interest (Fortin et al., 2018).

2.9 Statistical analysis

We used linear mixed-effects models (LMERs; *lme4* package; R version 4.0.3 via RStudio version 2021.09.1; R Core Team, 2020) in all analyses, included a random offset per participant to account for longitudinal repeated measures. For analyses of both AS performance (percent correct and latency on correct trials) and fronto-striatal rsFC (for each ROI pair), we first assessed the best fitting functional form of age by performing model selection (using AIC) while testing linear, inverse, and two quadratic functions (one with mean centered age-squared term, and another using a second order polynomial without a mean-centered term). If the AIC was equivalent (difference <2) among the best models, age effects were characterized with an inverse age function given previous research showing that trajectories in cognitive performance increase during adolescence, stabilizing into adulthood (Luna et al., 2004; Murty et al., 2018; Ordaz et al., 2013; Simmonds et al., 2017).

In each case (AS performance and rsFC), we then tested the effects of pubertal maturation (PDS, see above) while controlling for both age (based on the best fitting functional form of age) and sex effects. Statistical models for the effects of pubertal stage were tested separately in male and female participants given well-characterized sex differences in the timing of pubertal onset and differential hormonal processes underlying neurodevelopmental maturation.

Finally, to test differential involvement of fronto-striatal rsFC in AS performance depending on pubertal stage, we used linear mixed effects models containing an age by sex interaction term. Johnson-Neyman plots were used to visualize the nature of significant interactions.

In all models considering the effects of age and/or puberty on rsFC data, left and right ROI pairs were included in a single model; striatal and PFC subregion hemisphere were included as within-participants factors given that we did not have a hypothesis regarding lateralization of effects (see (Tervo-Clemmens et al., 2017). In all analyses, a random effect term for subject ID was included to account for repeated (longitudinal & hemispheric) measures. When assessing age-related change in rsFC, significance values were corrected using the Bonferroni method based on the six rsFC ROI pairs ($p<0.0083$). We employed a similar multiple comparison correction approach for the puberty analyses.

Results

3.1 Antisaccade (AS) performance and latency improves with age

AS performance improved significantly with age ($\beta = .43$, $t = 5.20$, $p < .001$), while correct latency significantly decreased significantly with age ($\beta = -.38$, $t = -4.12$, $p < .001$) in the pubertal sample (see **Figure 4**). There were no significant age-by-sex interaction effects for AS performance ($\beta = .24$, $t = 1.46$, $p = .146$) or latency ($\beta = .03$, $t = .18$, $p = .857$) in this sample. We found that puberty did not explain additional variance in either performance ($\beta = .04$, $t = .34$, $p = .732$) or correct response latency ($\beta = .08$, $t = .55$, $p = .581$) above and beyond the age effects, suggesting that age and puberty may be capturing largely similar variance in our sample, consistent with previous findings (Ordaz et al., 2017). When testing puberty-by-sex interactions and controlling for age effects, we did not observe a significant interaction effect on either AS performance ($\beta = 0.22$, $t = 1.37$, $p = .175$) or correct latency ($\beta = 0.14$, $t = 0.73$, $p = .467$).

Age-related improvements in AS performance and latency on correct trials were similar in the full (8-34-year-old) sample (see **Supplemental Figure S2** for details).

3.2 Fronto-striatal resting-state functional connectivity

PFC – NAcc connectivity pairs were best fit by an inverse age function per AIC values, for both males and females in the pubertal sample (ages 10 -18). The same was true when tested within the full sample (ages 8 – 34), except for anterior vmPFC –NAcc rsFC in females, for which age fitted with a mean-centered quadratic function performed the best.

When selecting the best function to fit puberty effects, we covaried for inverse age, given the results above. In males, puberty was best fit using an inverse function for all PFC – NAcc connectivity pairs except for dlPFC – NAcc, for which a mean-centered quadratic was the best performing model. In females, puberty was best fit by an inverse function for the following PFC subregional connections with the NAcc: anterior vmPFC, rACC, and vACC. The best performing model for the dlPFC – NAcc connection was a second-order polynomial function (without a mean-centered term). For the remaining two PFC connections with the NAcc (i.e., sgACC and vlPFC), a mean-centered quadratic function performed the best.

To test for significant associations between pubertal development and rsFC, we tested each connection for age and puberty effects simultaneously, including the best fitting form of age as a covariate, to identify the contribution of pubertal stage above and beyond any association with chronological age. We found a significant association between puberty and dlPFC – NAcc rsFC in both males (puberty^2; $\beta = .18$, $t = 3.46$, $p < .001$, $p_{\text{Bonferroni}} = .007$) and females (puberty^2; $\beta = 1.55$, $t = 3.26$, $p = .001$, $p_{\text{Bonferroni}} = .015$). Pubertal effects were best fit by a mean-centered quadratic function indicating an inflection point around mid-puberty (approximately transformed-PDS 3.5 males and 3.0 in females) increasing with pubertal stage. No other connections were significantly associated with puberty in males (all ps > .05). In females, we identified an additional association for vlPFC – NAcc connectivity (puberty^2; $\beta = .30$, $t = 4.99$, $p < .001$, $p_{\text{Bonferroni}} < .001$), which in males was not significant (puberty^{-1}; $\beta = .13$, $t = 1.48$, $p = .141$, $p_{\text{Bonferroni}} = 1.00$). Inspection of vlPFC – NAcc rsFC in females indicated an inflection point around late puberty (approximately transformed-PDS 4) reflecting increases in early pubertal stages. No other connections were associated with puberty in females (all ps > .05), although trend level (uncorrected significant) associations were noted for rACC – NAcc (puberty^{-1}; $\beta = -.08$, $t = -.71$,

$p = .011$, $p_{Bonferroni} = .132$) and sgACC – NAcc connectivity (puberty^{-1}; $\beta = -.15$, $t = -2.68$, $p = .008$, $p_{Bonferroni} = .096$). See **Table 1** and **Figure 5** for puberty-related effects associated with fronto-striatal functional maturation after controlling for age effects for model statistics and model fit visualizations, respectively, and **Supplemental Table S1** for main effects of sex and age, as well as interaction effects, on fronto-striatal functional maturation in the full sample (ages 8 - 34).

3.4 Antisaccade associations with fronto-striatal rsFC

To characterize the contribution of puberty-associated NAcc functional connectivity to the development of inhibitory control, we tested for associations between AS performance measures and connectivity strength among connections that were identified as having a pubertal contribution in the preceding analysis (i.e., dlPFC and vlPFC).

We observed a significant interaction between pubertal stage and percent correct on dlPFC – NAcc rsFC ($\beta = .10$, $t = 2.04$, $p = .041$), such that up until mid-puberty (transformed-PDS 3.6), greater connectivity was associated with lower percent of correct responses. This connectivity-performance association was no longer significant later in pubertal maturation (i.e., after transformed-PDS 3.6). There was no latency by puberty interaction effect on dlPFC – NAcc rsFC ($\beta = -.02$, $t = -.40$, $p = .687$). We observed a similar significant interaction in the larger sample on dlPFC – NAcc rsFC ($\beta = -.12$, $t = -4.65$, $p < .001$), and Johnson-Neyman plots showing this interaction effect (**Figure S3**) indicated that at older ages (e.g., after age 15), increased connectivity was associated with poorer antisaccade performance. We identified a significant latency by puberty interaction on vlPFC – NAcc rsFC ($\beta = -.14$, $t = -2.51$, $p = .012$), such that in early puberty (prior to transformed-PDS 2.9), greater connectivity was associated with longer/slower latency on correct trials. There was no association later in pubertal maturation (i.e., after transformed-PDS 2.9). See **Figure 6** for Johnson-Neyman plots of interaction effects of puberty and antisaccade performance and latency in dlPFC – NAcc (a) and vlPFC – NAcc (b), respectively. There was no effect of puberty and percent correct performance on vlPFC – NAcc rsFC ($\beta = .02$, $t = .38$, $p = .703$).

Discussion

In this study, we used longitudinal rsfMRI neuroimaging data to investigate puberty-related associations with fronto-striatal rsFC maturation—over-and-above age-related contributions—and tested associations with response inhibition using the antisaccade task. We focused our analyses on functional connectivity of the NAcc, with regions supporting cognitive and motivational processes (Harsay et al., 2011; Paulsen et al., 2015). Using data from a harmonized, longitudinal sample we focused on ages 10 - 18 when puberty progresses, and tested puberty-related maturational changes in fronto-striatal rsFC and response inhibition to (1) characterize the specific pubertal contributions to developmental changes across these networks and (2) identify potential mechanisms for fronto-striatal maturation supporting development of inhibitory control behaviors. We found that pubertal maturation was associated with increases in connectivity between the lateral, but not medial, PFC and NAcc above and beyond the effects of age, with both dlPFC and vlPFC (in females). Importantly, these connections differentially predicted behavior during later puberty with dlPFC – NAcc connectivity showing associations with improvements in rate of inhibitory responses and vlPFC – NAcc showing associations with the latency to execute an inhibitory response.

We found that puberty showed a strong association with increases in dlPFC – NAcc rsFC while chronological age in 10-18 was only associated with increases in connectivity in females. The limited association with age is not surprising, given the longer trajectories of specialization seen well into the 20s and 30s ((Parr et al., 2021), **Figure S4**) including our own extended data with NAcc and anterior vmPFC, sgACC, rACC, vACC, and dlPFC. Given these age-related increases in dlPFC – NAcc rsFC, the additional association with puberty suggest that it may influence specialization as a scaffold for continued age-related maturation beyond puberty into adulthood. This is supported by our observation of a "shift" (i.e., the inflection point in quadratic-fitted puberty models) around mid-late puberty. Importantly, we found that increased dlPFC – NAcc rsFC was associated with the rate of correct inhibitory responses. The dlPFC is well established as core to cognitive processes, including inhibitory control (Angius et al., 2019) but also working memory (Arnsten and Jin, 2014), action selection (Mars and Grol, 2007), attentional processes (Johnson et al., 2007), and cognitive effort expenditure (Framorando et al., 2021). Past studies have indicated that activation of dlPFC does not explain improvements in error responses in the antisaccade task as it is recruited similar to adults (Ordaz et al., 2013). These results suggest that while local function of dlPFC may be in place by adolescence, its connectivity to motivated action regions such as the NAcc may be particularly influenced by pubertal change, especially in late puberty supporting the ability to sustain a high rate of inhibitory responses. As the ability to generate a high rate of inhibitory responses increases into mid-adolescence enhanced integration with NAcc may propel consistent inhibitory responses into adulthood as a surge in gonadal sex hormones takes place (Balzer et al., 2019), which we may underlie the significant switch to increased dlPFC – NAcc connectivity at this later time in development.

Pubertal maturation was also associated with vlPFC – NAcc rsFC in females while not associated with age from 10-18. As with dlPFC, vlPFC also shows continued age-related improvements through young adulthood (Paulsen et al., 2015) suggesting a possible unique puberty driven specialization during this window of adolescence that is particularly linked to female puberty. Importantly, we found that increased vlPFC – NAcc rsFC was associated with response latency on correct antisaccade trials during earlier pubertal stages. This is consistent with past evidence indicating that latency of antisaccade responses matures earlier in adolescence than

percent of correct inhibitory responses (Luna et al., 2004). We also found an association between antisaccade task-related vlPFC – cingulate connectivity and pubertal stage and correct trial latency in a subset of our data (Ravindranath et al., 2022) further supporting this result. Previous work has found that the vlPFC underlies the formation of the association between visual cues and action selection (Passingham et al., 2000) and optimal performance (Paulsen et al., 2015).

Sex differences in hormonal changes during puberty may underlie our results of the association between vlPFC – NAcc rsFC and response latency. Estradiol and progesterone in females have been found to support inhibitory control (Wang et al., 2020), and estradiol has been found to be positively associated with striatal activation during reward outcome (Macks et al., 2011) and dlPFC engagement (Chung et al., 2019). Puberty has also been found to not be associated with reward circuitry in boys ref. Separate work has also shown that more advanced pubertal maturation is associated with reduced striatal activation during reward outcome relative to same-age, but less pubertally advanced, peers (Forbes et al., 2010). The same study also observed a significant positive association between testosterone and striatal activation in boys during reward anticipation but a negative association between testosterone and striatal activation in boys and girls during reward outcome, suggesting that hormone-neural coupling may differ as a function of pubertal development. These studies suggest that vlPFC – NAcc rsFC may underlie the ability to readily execute cognitive control specifically in females as a unique pathway for maturation of execution of inhibitory control as sex differences are not found in antisaccade performance (Ordaz et al., 2017). Males may have a unique trajectory or a different timing of maturation of this circuitry.

Interestingly, we did not observe pubertal associations with NAcc rsFC to medial PFC regions reported in previous studies (Barendse et al., 2020; Pfeifer et al., 2013). Medial and orbital PFC structures have been found to develop earlier in development than lateral PFC subregions in primates (Caviness et al., 1995; Orzhekhovskaia, 1977, 1975). Given that our sample was skewed towards more pubertally advanced participants, we may have failed to detect puberty-brain associations occurring earlier in development, such as those involving medial PFC and ACC regions, which may occur at initial stages of puberty.

Notably, along with its role in response inhibition (Aron et al., 2004; Blasi et al., 2006), the vlPFC is also centrally involved in emotion regulation processes (Phillips et al., 2008; Picó-Pérez et al., 2017; Silvers et al., 2016). This is of potential interest given the marked sex-related divergence in prevalence of *affective* disorders during this time, when adolescent females are, on average, about twice as likely as adolescent males to develop mood and anxiety disorders (Angold and Worthman, 1993), possibly reflecting differences in neural circuit maturation as a function of sex hormones (Sisk and Zehr, 2005). Evidence implicates vlPFC – NAcc connectivity in affective development (Wager et al., 2008) and separate work suggests sex-specific roles for cortical thinning in lateral PFC subregions (i.e., dlPFC, vlPFC) in cognitive aspects of emotion regulation in female participants (Vijayakumar et al., 2014). However, few studies have considered the influence of puberty on the vlPFC (although see (Forbes et al., 2011; Ladouceur, 2012)). Although less implicated in affective processes than the vlPFC, the dlPFC has also been suggested to be involved in certain aspects of emotion regulation and reactivity (Clarke et al., 2020). The relationship between pubertal changes in fronto-striatal connectivity and affective development therefore reflects an important area for future study.

Although specific mechanisms remain unknown, investigators have posited that a confluence of exposure to hormones (e.g., testosterone, estradiol) and psychosocial stress and stimulation (e.g., new romantic interests, academic or work-related demands) are likely to act in

conjunction during this critical period of cortico-subcortical (e.g., fronto-striatal) neurodevelopment (Byrne et al., 2017; Larsen and Luna, 2018; Sinclair et al., 2014), potentially explaining the increased prevalence of psychiatric disorders during this period (Paus et al., 2008; Ullsperger and Nikolas, 2017). Several lines of evidence implicate dopaminergic systems as one key link between puberty—and gonadal sex hormones, in particular—and neurodevelopment supporting cognitive maturation (Hernandez et al., 1994; Kuhn et al., 2009; Ladouceur et al., 2018). Findings from experiments carried out in animal models suggest that puberty and dopaminergic neurophysiological maturation not only overlap in their developmental timelines, but center puberty as a potentially necessary factor for maturation of dopaminergic circuitry and goal-directed behaviors (Bell et al., 2013). Animal models have shown that dopamine can inhibit pubertal hormone synthesis (i.e., luteinizing hormone), and increased dopamine receptor binding correlates with testosterone levels, particularly in females (Andersen et al., 2002), suggesting an intricate interplay between these two systems that may support the transition from adolescence to adulthood (Vidal et al., 2004). Along with the now well-characterized maturation of PFC systems during human adolescence (e.g., (Caballero et al., 2016; Luna et al., 2001)), the dopaminergic system—centrally implicated in motivated behaviors and risk-taking (e.g.,(Macks et al., 2016; Parr et al., 2021)—simultaneously embarks on its own period of rapid specialization to support adult-like cognitive processes (Cools et al., 2019; Larsen et al., 2020; Larsen and Luna, 2018). Alongside cognitive improvements, dopaminergic neurophysiology is also thought to underlie canonical behaviors that characterize the adolescent period like sensation-seeking and risk-taking (Cohen et al., 2010; Duijvenvoorde et al., 2014; Steinberg, 2008). Developmental changes in dopaminergic fronto-striatal circuitry may also underlie risk for major psychopathologies, several of which emerge during the adolescence period, including substance use disorders (Chambers et al., 2003), depressive and anxiety disorders (Auerbach et al., 2014; Ho, 2021), and schizophrenia (Murray et al., 2008).

Study limitations and strengths

Our findings should be considered in light of several limitations. First, our puberty measure was self-reported. Evidence suggests that although self-report measures and clinical physical assessment correspond, there are some caveats in using only the former: specifically, whereas boys tend to report being more pubertally advanced compared to clinical assessments, girls tend to underreport their pubertal stage (Rasmussen et al., 2014). Critically, we also only examined associations in individuals in whom pubertal maturation was already underway (transformed-PDS ≥ 2) and our sample was negatively skewed, such that more pubertally mature adolescents were overrepresented, limiting our ability to detect and interpret effects associated with earlier periods of adolescence and puberty. In line with this limitation, these maturational effects captured in older participants (i.e., ages 10 and older) are likely more prominent in female participants as compared to male participants, given earlier pubertal maturation in females (Patton and Viner, 2007). Future studies would benefit from longitudinal, multimodal datasets—such as those collected in the Adolescent Brain Cognitive Development ("ABCD") study—to ensure that the present results are replicated and extended in a larger and more diverse sample to better generalize our findings.

Despite these limitations, our study has several considerable strengths. First, our study leveraged two large, longitudinal, multimodal datasets to test linear and non-linear pubertal contributions to fronto-striatal functional connectivity. We focused our analyses on pubertal *maturation* by only including participants with PDS ≥ 2 to ensure that the maturational processes

of interest were already underway. Additionally, our large extended (full) sample (ages 8 – 34) with several longitudinal timepoints allowed us to track developmental trajectories through adolescence and into early adulthood thereby situating our findings in the context of adult fronto-striatal circuitry more broadly. This is crucial given that although we only observed one significant age effect in the puberty sample, when considering the larger sample, we observed several significant age-related associations with fronto-striatal rsFC. Finally, by examining both medial and lateral PFC subregional connections with the NAcc, we show for the first time, to our knowledge, that puberty likely influences lateral PFC-NAcc circuit development as well, which, in turn, supports cognitive processes such as inhibitory control during adolescence.

Conclusions & future directions

Our findings add to a nascent yet growing body of scientific literature investigating the effects pubertal maturation has on the developing adolescent brain. Notably, our results highlight specific connections that may be influenced by puberty-related processes. The present findings identify fronto-striatal connections that are puberty-specific (e.g., vlPFC-NAcc in females and dlPFC-NAcc in males and females) and others that exhibited age effects in the full sample but failed to exhibit puberty associations (e.g., medial/ACC regions). This, in particular, may suggest that some fronto-striatal maturational effects are specific to pubertal processes whereas others are not. These results suggest that maturation related to puberty may add specific specialization supporting later maturation into adulthood. Given the sex specificity of some of our findings (e.g., vlPFC-NAcc), we believe this work may inform differential sex-related risks of psychopathology that emerge during this time. Finally, our results underscore the importance of looking at pubertal change including the mechanistic role of hormones especially when interested in unique processes of adolescent development.

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Figures

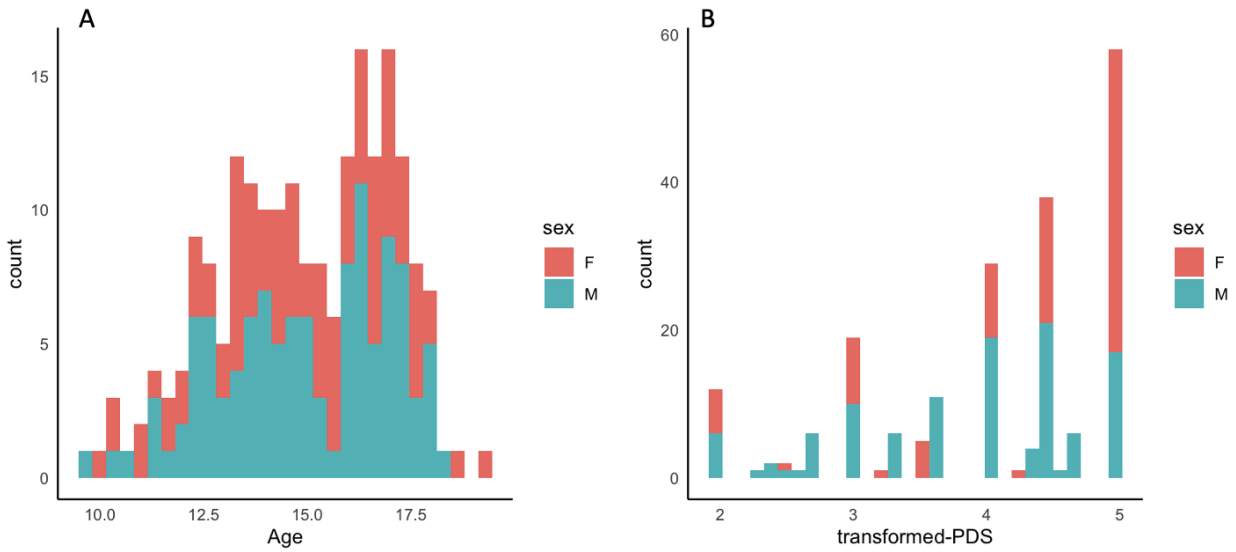

Figure 1. Distribution of participant characteristics with puberty data by (A) age and (B) transformed-PDS scores, separated by sex.

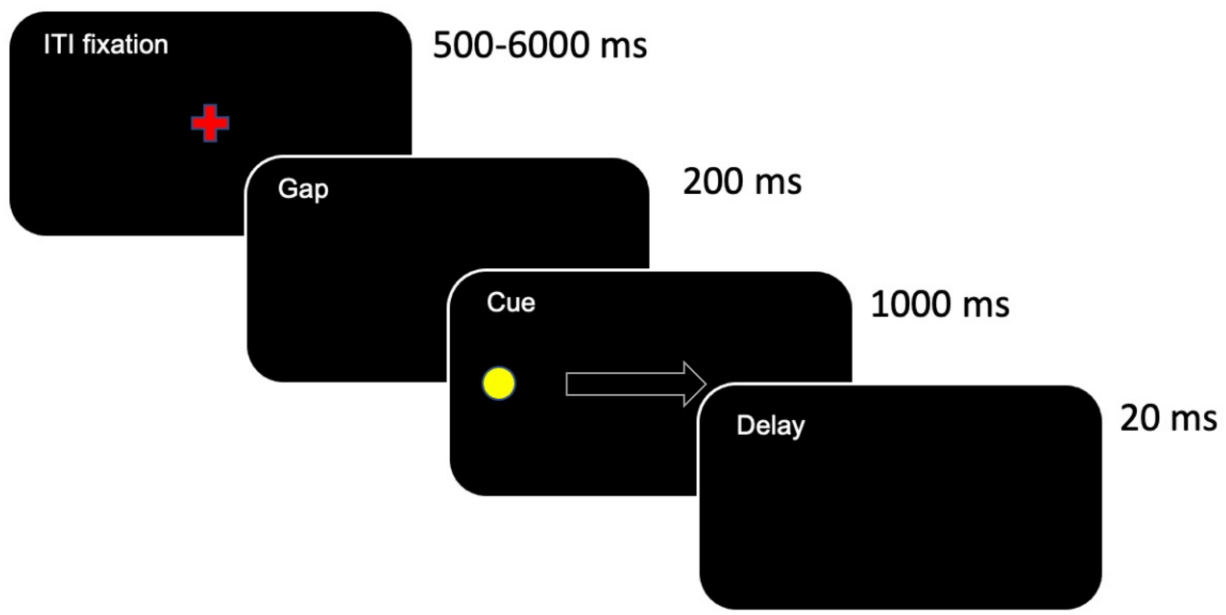

Figure 2. Antisaccade task schematic.

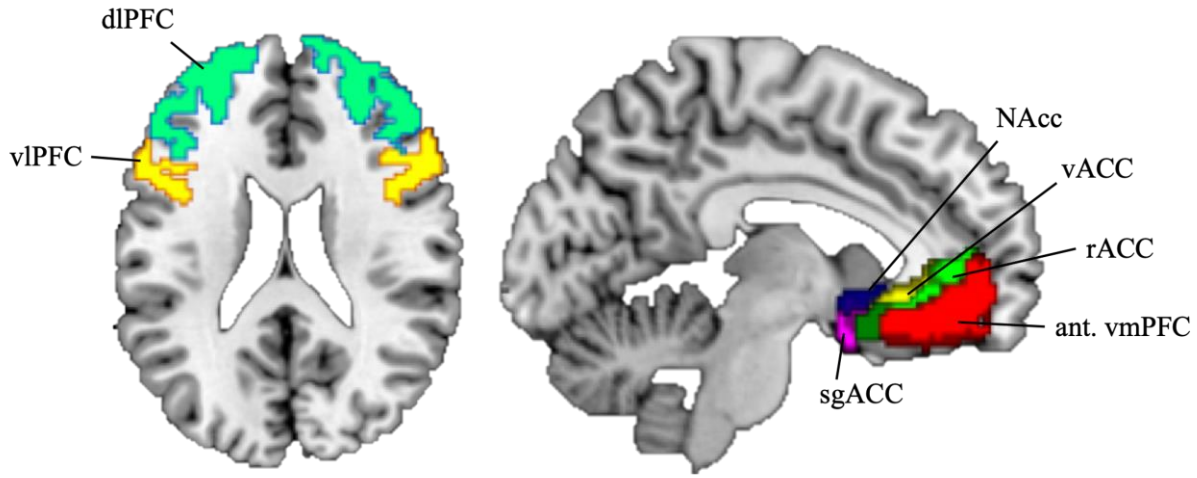

Figure 3. Fronto-striatal regions of interest (ROIs). Abbreviations: NAcc, nucleus accumbens; vmPFC, ventromedial prefrontal cortex; sgACC, subgenual cingulate; vACC, ventral anterior cingulate cortex; rACC, rostral anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

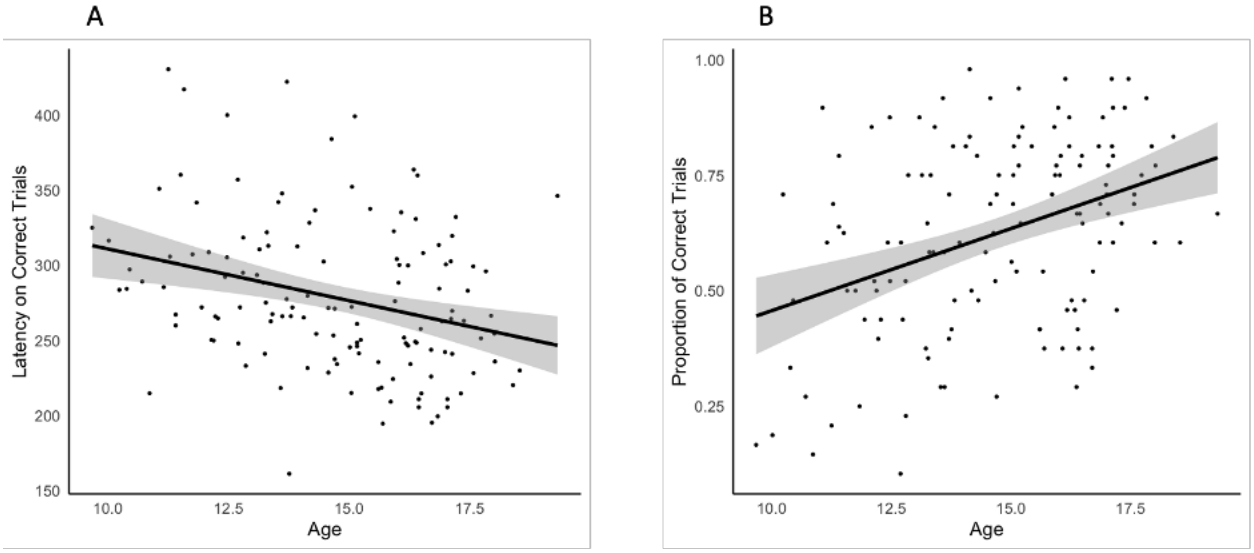

Figure 4. Age effects in the puberty sample on antisaccade mean latency (A) and performance (percent correct) on correct trials (B).

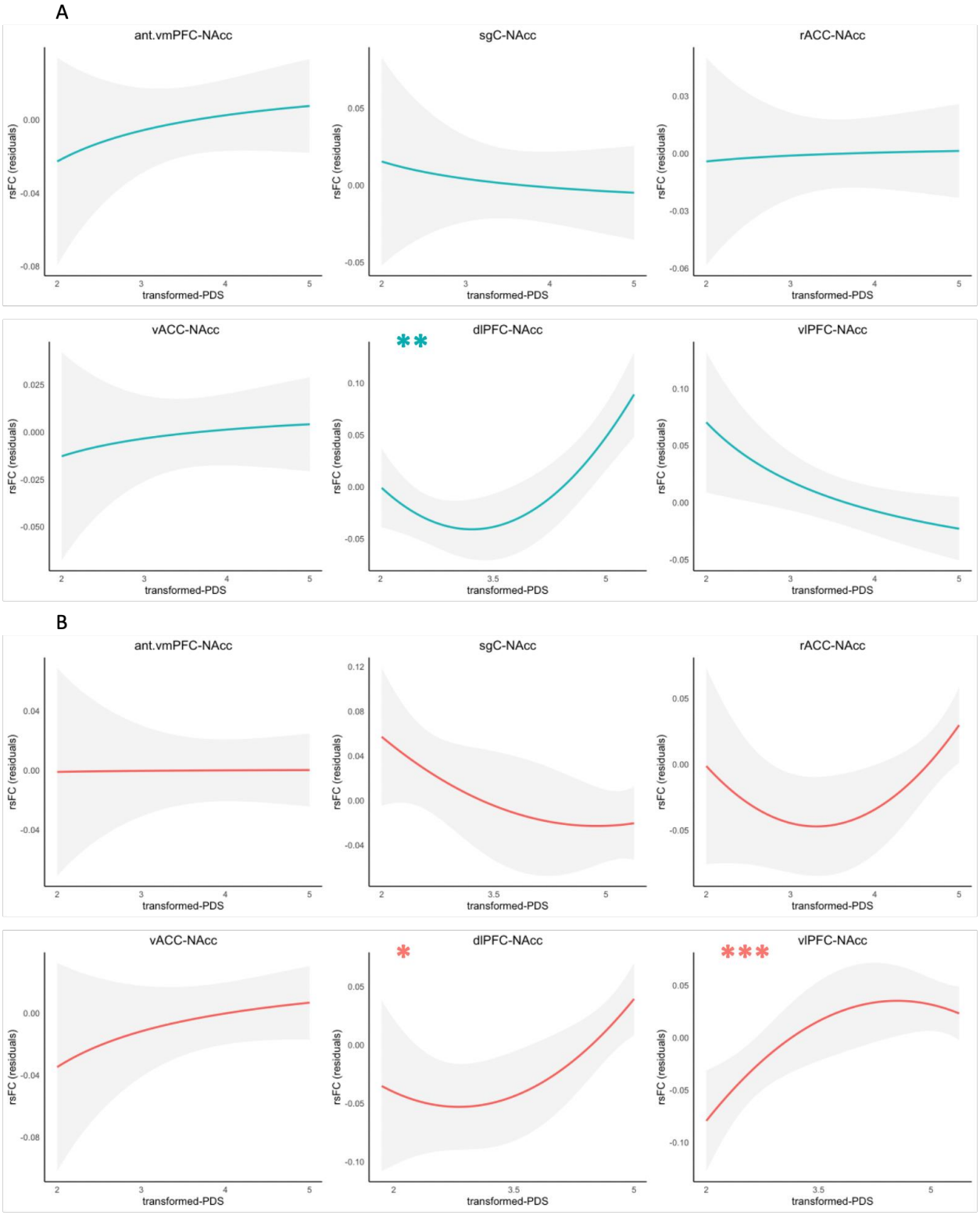

Figure 5. Puberty-related fronto-striatal resting-state functional connections in (A) males and (B) females. Depicted best fit models have regressed out age effects for visual clarity. Abbreviations:

ant.vmPFC, anterior ventromedial prefrontal cortex; sgC, subgenual anterior cingulate cortex; rACC, rostral anterior cingulate cortex; vACC, ventral anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; NAcc, nucleus accumbens; rsFC, resting-state functional connectivity.

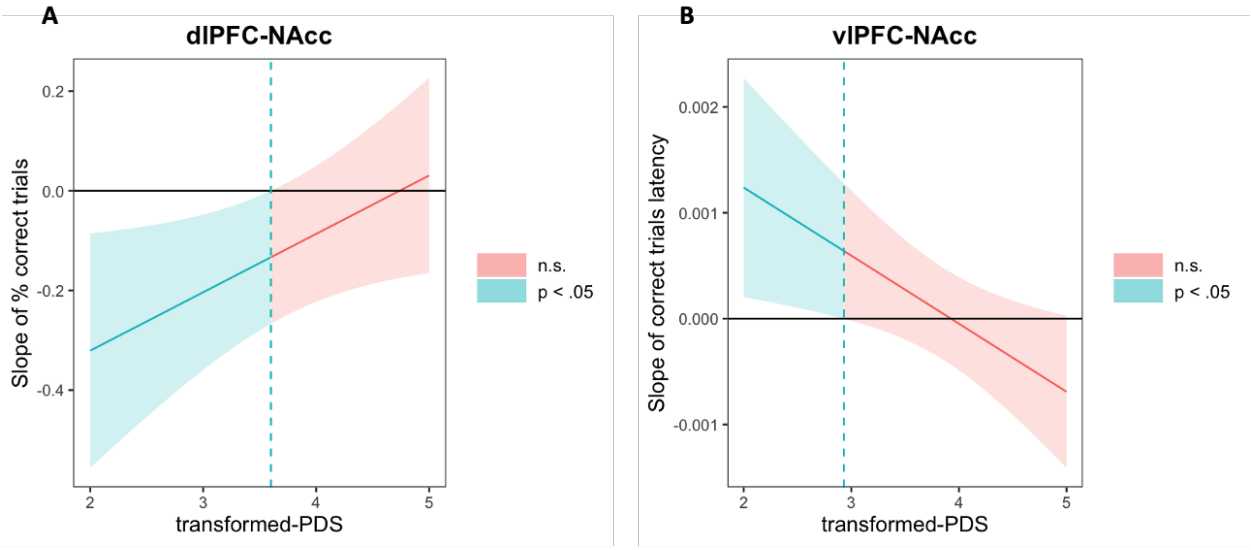

Figure 6. Johnson-Neyman plots showing periods of pubertal maturation during which there is a significant effect of dlPFC-NAcc connectivity on antisaccade performance (i.e., percent of correct trials) (A) and vlPFC-NAcc connectivity on antisaccade correct trial latency after controlling for age and sex effects (B).

Supplemental Figures

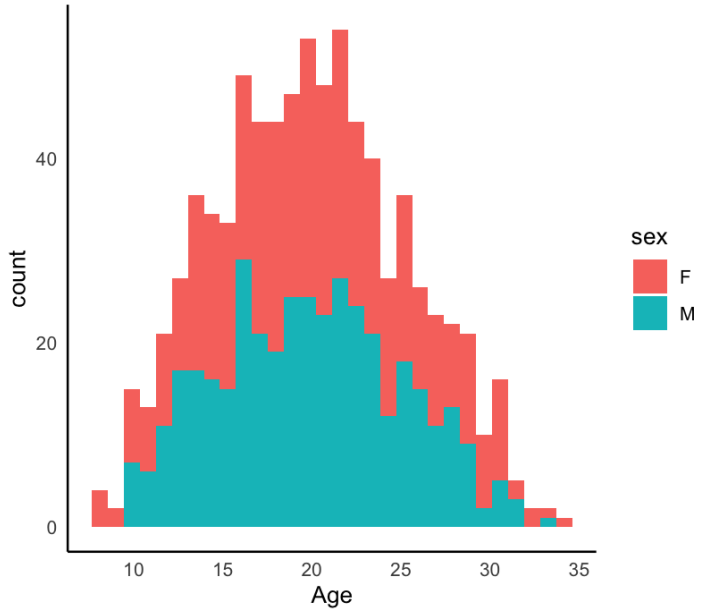

Figure S1. Age distribution of participants in the extended sample.

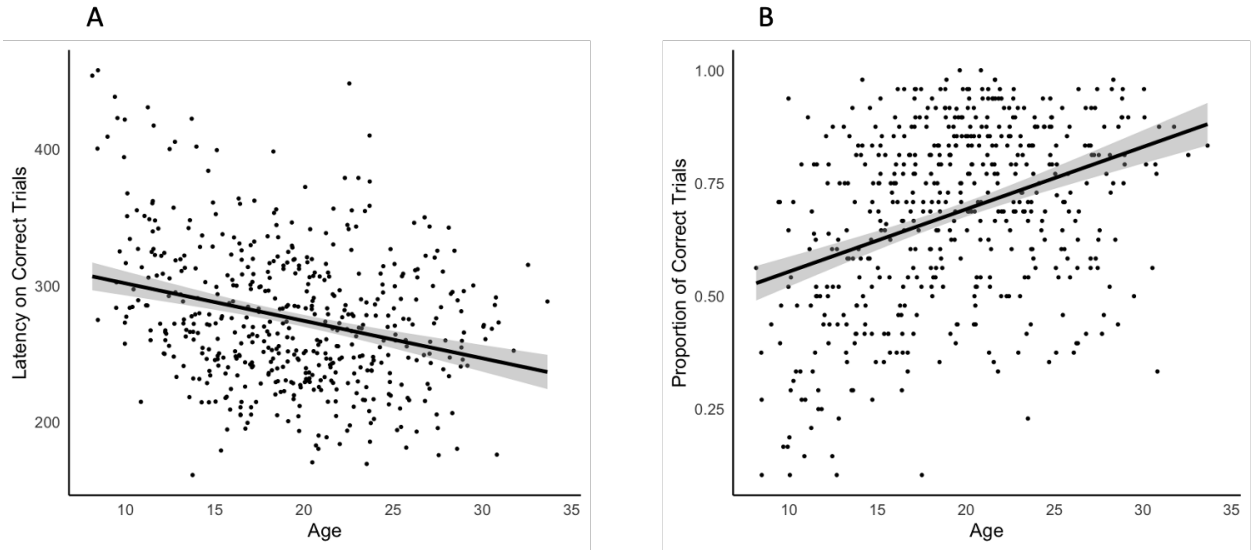

Figure S2. Antisaccade task performance on correct trials in full age sample by (A) latency on correct trials and (B) proportion of correct trials.

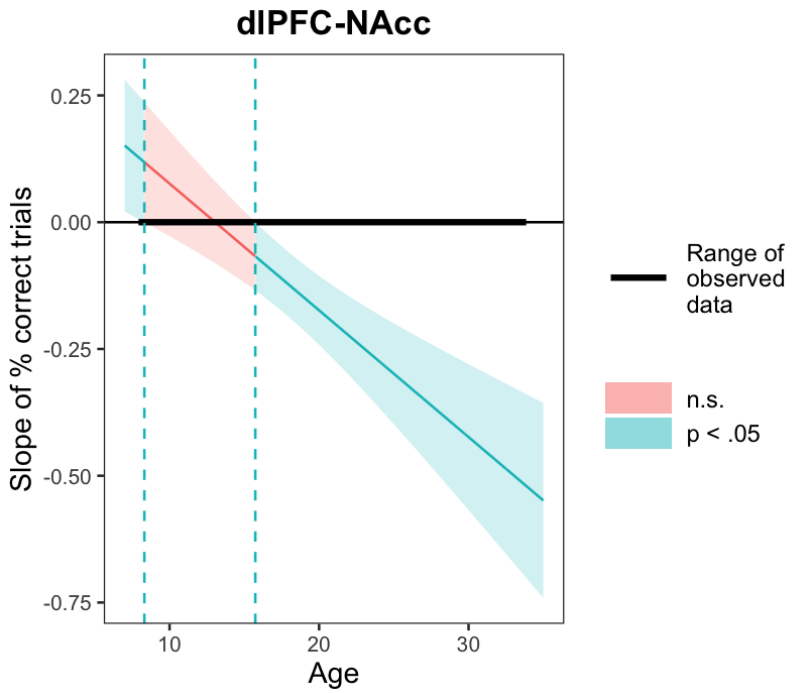

Figure S3. Johnson-Neyman plot showing age during which there is a significant effect of dlPFC-NAcc connectivity on antisaccade performance (i.e., percent of correct trials) and controlling for sex.

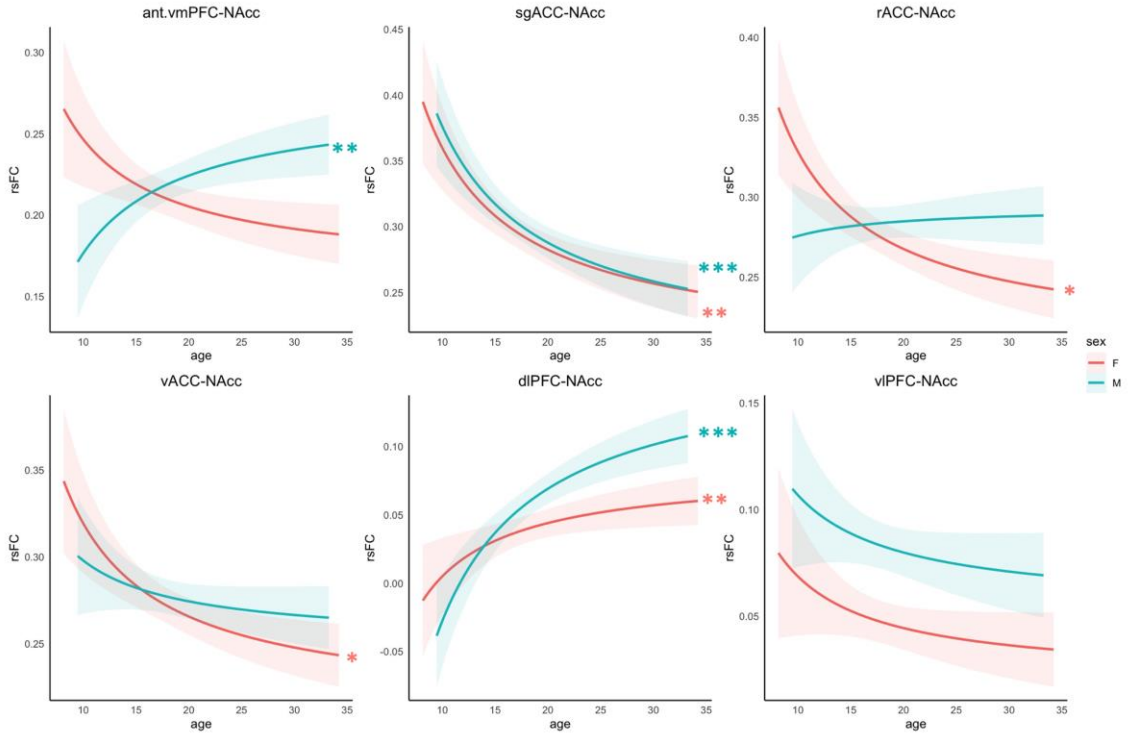

Figure S4. Age effects in the extended sample. * $p < .05$, ** $p < .01$, *** $p < .001$

Tables

Table 1. Best performing statistical models testing puberty effects on fronto-striatal resting-state functional connectivity after controlling for age^{-1} effects.

Note: best model fits were determined using AIC. $p < .05$ are bolded. * indicates mean-centered quadratic fit.

Abbreviations: ant. vmPFC, anterior ventromedial prefrontal cortex; sgACC, subgenual anterior cingulate cortex; rACC, rostral anterior cingulate cortex; vACC, ventral anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

A. Models in male participants

Connection	Variable	β (95% CI)	t	p	p_{Bonf}
ant. vmPFC – NAcc	puberty^{-1}	-.10 (-.27, .08)	-1.08	.280	1.00
sgACC – NAcc	puberty^{-1}	.01 (-.15, .18)	.16	.871	1.00
rACC – NAcc	puberty^{-1}	-.14 (-.31, .04)	-1.56	.120	1.00
vACC – NAcc	puberty^{-1}	-.07 (-.24, .10)	-.83	.405	1.00
dlPFC – NAcc	puberty^{2*}	.18 (.08, .29)	3.46	**< .001**	**.007**
vlPFC – NAcc	puberty^{-1}	.13 (-.04, .26)	1.48	.141	1.00

B. Models in female participants

Connection	Variable	β (95% CI)	t	p	p_{Bonf}
ant. vmPFC – NAcc	puberty^{-1}	-.09 (-.26, .08)	-.99	.324	1.00
sgACC - NAcc	puberty^{2*}	-.15 (-.26, -.04)	-2.68	**.008**	.096
rACC – NAcc	puberty^{-1}	-.22 (-.38, -.05)	-2.56	**.011**	.132
vACC – NAcc	puberty^{-1}	-.14 (-.30, .03)	-1.60	.110	1.00
dlPFC – NAcc	puberty^{2}	1.55 (.61, 2.48)	3.26	**.001**	**.015**
vlPFC – NAcc	puberty^{2*}	.30 (.18, .42)	4.99	**< .001**	**< .001**

Supplemental Tables

Table S1. Best performing statistical models testing age effects on fronto-striatal resting-state functional connectivity in full sample (ages 8-34).

Note: best model fits were determined using AIC. Non-significant age by sex interaction terms were dropped from models (denoted by *n.s.*). Significant *p*-values are bolded.

Abbreviations: ant. vmPFC, anterior ventromedial prefrontal cortex; sgACC, subgenual anterior cingulate cortex; rACC, rostral anterior cingulate cortex; vACC, ventral anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

Connection	Variable	β (95% CI)	t	p	p_{Bonf}
ant. vmPFC – NAcc	age^{-1}	.03 (-.03, .10)	.98	.328	1.00
	sex	.05 (-.11, .20)	.58	.565	1.00
	age^{-1} * sex	-.14 (-.24, -.04)	-2.65	**.008**	**.032**
sgACC – NAcc	age^{-1}	.13 (.08, .17)	5.35	**< .001**	**< .001**
	sex	.01 (-.12, .14)	.16	.870	1.00
	age^{-1} * sex			n.s.	
rACC – NAcc	age^{-1}	.07 (.01, .14)	2.26	**.024**	.144
	sex	.10 (-.05, .24)	1.30	.194	1.00
	age^{-1} * sex	-.13 (-.22, -.03)	-2.49	**.013**	.052
vACC – NAcc	age^{-1}	.08 (.02, .15)	2.59	**.010**	.060
	sex	.05 (-.09, .18)	.66	.508	1.00
	age^{-1} * sex	-.14 (-.23, -.04)	-2.72	**.006**	**.024**
dlPFC – NAcc	age^{-1}	-.09 (-.15, -.02)	-2.66	**.008**	**.048**
	sex	.11 (-.03, .25)	1.49	.136	.816
	age^{-1} * sex	-.11 (-.21, -.01)	-2.21	**.027**	.108
vlPFC – NAcc	age^{-1}	.01 (-.03, .06)	.60	.546	1.00
	sex	.19 (.05, .33)	2.68	**.007**	**.042**
	age^{-1} * sex			n.s.	

Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: